

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 090218

Name: Glatopa (Glatiramer Acetate) Injection,
20 mg/mL, 1 mL prefilled syringe

Sponsor: Sandoz, Inc.

Approval Date: April 16, 2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090218

CONTENTS

Reviews / Information Included in this ANDA Review

Approval Letter	X
Other Action Letters	X
Labeling	X
Labeling Reviews	X
REMS	
Medical Reviews	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Reviews	
Microbiology Reviews	X
Other Reviews	X
Proprietary Name Reviews	X
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090218

APPROVAL LETTER



ANDA 090218

Sandoz, Inc.
2555 West Midway Blvd.
Broomfield, CO 80038
Attention: Jean Domenico
Associate Director, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 27, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Glatopa (Glatiramer Acetate) Injection, 20 mg/mL, 1 mL prefilled syringe.

Reference is also made to the Complete Response letter issued by this office on August 19, 2014, and to your amendments dated October 1 and November 17, 2014.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. **Accordingly the ANDA is approved**, effective on the date of this letter. The Office of Generic Drugs has determined your Glatopa (Glatiramer Acetate) Injection, 20 mg/mL, 1 mL prefilled syringe meets the standards for approval (including those for active ingredient sameness and bioequivalence) and, therefore, is therapeutically equivalent to the reference listed drug product (RLD), Copaxone® (Glatiramer Acetate) Injection, 20 mg/mL, 1 mL prefilled syringe, of Teva Pharmaceuticals USA.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory

requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

You have been requested to provide information after the drug application has been approved. Any information submitted to meet the conditions requested in this letter is considered a “Post Approval Commitment Response”. To alert the Office of Generic Drug staff to the fact that you are providing post approval commitment information, please designate your submission in your cover letter as “POST APPROVAL COMMITMENT RESPONSE”.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>,

that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

<http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.


The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

William P.

Rickman -S

Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research



Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300043242, cn=William P. Rickman -S
Date: 2015.04.16 11:11:36 -0400

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

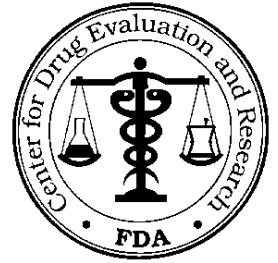
ANDA 090218

OTHER ACTION LETTERS

COMPLETE RESPONSE

ANDA 090218

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: Sandoz, Inc.

TEL: 303-438-4242

ATTN: Jean Domenico
Associate Director, Regulatory Affairs

FAX: 303-438-4600

FDA CONTACT PHONE: 240-402-8932

FROM: Simon Eng

Dear Madam:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (9 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.



ANDA 090218

COMPLETE RESPONSE

APPLICANT: Sandoz, Inc.
Attention: Jean Domenico
Associate Director, Regulatory Affairs
2655 West Midway Boulevard
Broomfield, CO 80038-0446

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 26, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatopa (Glatiramer Acetate Injection), 20 mg/mL, 1 mL prefilled syringes.

We acknowledge receipt of your amendments dated February 28, March 12, March 26, April 3, May 12, June 10 and June 18, 2014. These submissions constituted a complete response to our February 14, 2014 action letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

A. Deficiencies

Review of Response to the Complete Response Letter issued on February 14, 2014

- 1.
- 2.
- 3.



Following this page, 5 pages withheld in full - (b)(4)

33. As part of CDER/OC/OMPQ review of the withhold recommendation from the district, please provide a signed statement that once the stability methods/testing matrix has been finalized in correspondence with OPS, that all methods will be verified at the facilities that will be performing those tests.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. As CDER has committed to address the technical issues regarding stability test methods, OMPQ does not concur with the (b) (4)-DO recommendation to withhold approval of ANDA 90218 due to product-specific deficiencies related to testing of Glatiramer acetate. However if you do not provide a signed statement as detailed above, or your response to OPS regarding stability testing is found inadequate, CDER/OC reserves the right to reverse the decision based upon updated information.
2. Please include a clear and appropriate storage conditions on the label for the drug substance Glatiramer Acetate.
3. Please provide the updated stability data for the validation batches 100M7278, 051M7282, 061M7276 and 071M7276. This data should contain stability studies results for long-term storage conditions at least up to (b) (4) months, since you are proposing (b) (4) months expiration period.
4. We recommend you to specify the acceptance limits for the yield of each manufacturing step and include those in the batch record.

BIOEQUIVALENCE

The Division of Bioequivalence has completed its review and has no further questions at this time. The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by the chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

MICROBIOLOGY (if appropriate)

The Division of Microbiology has no further questions at this time.

LABELING

The Labeling Review Branch has no further questions/comments at this time based on your labeling submission dated March 26 and April 3, 2014.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

FACILITY INSPECTIONS

Office of Compliance has no further questions at this time. The compliance status of each facility named in the application may be re-evaluated upon re-submission.

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESUBMISSION/ **MINOR COMPLETE RESPONSE AMENDMENT/CHEMISTRY**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce

or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Simon Eng, Regulatory Project Manager, at (240) 402-8932.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, Pharm.D.
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

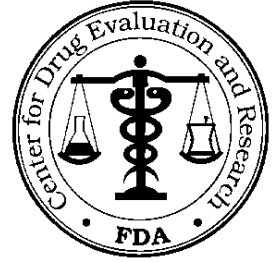
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AARON W SIGLER on behalf of DENISE T MCKAN
08/19/2014

COMPLETE RESPONSE

ANDA 090218



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TO: Sandoz Inc.

TEL: 303-438-4242

ATTN: Jean Domenico

FAX: 303-438-4600

FROM: Simon Eng

FDA CONTACT PHONE: 240-276-8529

Dear Madam:

This facsimile is in reference to your abbreviated new drug application, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

We have completed the review and have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (___ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.



ANDA 090218

**COMPLETE RESPONSE
MAJOR**

Sandoz Inc.
Attention: Jean Domenico
Associate Director, Regulatory Affairs
2555 West Midway Blvd.
Broomfield, CO 80038

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/1 mL, dispensed in single dose glass syringe with needle.

We acknowledge receipt of your amendments dated May 4, 2009; April 30, 2010; July 20, July 21, August 9 and October 27, 2011; February 21, June 13, June 22, July 13, September 25, October 26, November 29 and December 10, 2012 and January 30, 2013. We further acknowledge receipt of your meeting requests and correspondences dated January 17, February 14, February 16, February 27, March 13, March 23, April 6, May 8 and May 29, 2012 and January 15 and April, 22, 2013.

We also refer to our Major Complete Response letter dated November 27, 2013 which contains the following error: the Microbiology section erroneously stated that the Division of Microbiology had no further questions.

This replacement Complete Response letter incorporates the correction of the error. Please resubmit a Complete Response amendment to include the Microbiology deficiencies as soon as possible.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies

We currently focus on the information you have provided regarding the drug substance manufacturing development and drug substance characterization relevant to the establishment of drug substance sameness for Glatiramer Acetate. We acknowledge your approach of demonstrating the sameness of your proposed drug substance to that in the RLD by understanding and identifying process-related structural signatures through systematic experimental investigation and mathematical modeling. However, there are still some uncertainties about interpretation and quality of some of your data sets. We believe that these uncertainties gave rise to the deficiencies, as summarized below. Upon addressing these deficiencies, we will undertake the review of remaining sections of the drug substance module, including biocharacterization and the drug product in your ANDA.

The manufacture and manufacturing process development of the drug substance have the following deficiencies

- 1.
- 2.
- 3.
- 4.



(b) (4)

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

1. Please provide samples of your drug substance, drug product, negative controls and the reference product.
2. We also recommend you (b) (4)

of Glatiramer Acetate.

BIOEQUIVALENCE

The Division of Bioequivalence has completed its review and has no further questions at this time. The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

MICROBIOLOGY

Microbiology Deficiencies:

1. DMF (b) (4) is deficient. The DMF holder has been notified.

2. (b) (4)

- 3.

4. Regarding the (b) (4) used in production:

Following this page, 1 page withheld in full - (b)(4)

10.

11.

(b) (4)

LABELING

1. GENERAL COMMENT *¹ - Your proprietary name labels and labeling are pending review and results may be communicated to you under separate coverage by the Reviewing Division. Should one of your proposed proprietary names become prior to full approval of your application, you may resubmit the requested labeling changes with the proprietary name. We acknowledge submission of established named labels and labeling on 6/25/2012 and will proceed with the labeling review. Should your proprietary name not be approved prior to full approval action, we will be able to use the established name labels and labeling towards final action.
2. CONTAINER DRUG PRODUCT: 20 mg/1 mL - Satisfactory. However, if space permits please add the Rx Only statement. Please provide a diagram and/or actual sample of your syringe.
3. ONE VIAL BLISTER -
 - a. Please add the needle information. Example. 1 mL single dose _____ syringe with attached _____ length and _____ gauge needle. In addition, add the type of syringe (ex: glass). We are aware the reference product does not include this information. However, since a needle is attached, as part of the package, we feel that information should be included on the labels.
 - b. The text on the blister is difficult to read because there is underlining text that can

*¹ We acknowledge our January 17, 2013 correspondence concerning our conditionally acceptable response to your proposed proprietary name request, Glatopa.

be seen from the viewing side of the blister. Please submit labeling that does not impede viewing the labeling on one side or the other.

4. CARTON: Include needle information.
5. PROFESSIONAL PACKAGE INSERT
 - a. Include needle information in the HOW SUPPLIED section and the type of syringe (glass, .etc)
 - b. There are areas of blue shade in the insert. Please correct and return the color to black. Example.... See Highlight content section. Please revise through out the insert.
 - c. Please monitor the Drugs@FDA website for updated labeling prior to submitting your amendment. Please site the reference listed drug NDA number, supplement number, and supplement approval date that your insert labeling is modeled after.
6. PATIENT INFORMATION SHEET- **Please** includes needle information.
 - a. Please revise your labeling, as instructed above, and submit electronically in draft or final print pdf format.
 - b. Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –
 - c. http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

FACILITY INSPECTIONS

We have not yet completed inspection(s)/compliance evaluation of your manufacturing facility(s) named or referenced in this ANDA. We must perform a complete evaluation of the information associated with the inspection before determining that the site(s) are satisfactory and this ANDA may be approved.

OTHER

A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

RESUBMISSION MAJOR COMPLETE RESPONSE AMENDMENT CHEMISTRY /LABELING /MICROBIOLOGY

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.65. You may also request an extension of time in which to resubmit the ANDA. A resubmission response must fully address all the deficiencies listed.

The drug product may not be legally marketed until you have been notified in writing that this ANDA is approved.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Simon Eng, Regulatory Project Manager, at (240) 276-8529.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

02/14/2014

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090218

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GLATOPA™ safely and effectively. See full prescribing information for GLATOPA™.

GLATOPA™ (glatramer acetate injection), for subcutaneous use
Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Dosage and Administration, Recommend Dose (2.1)	01/2014
Dosage and Administration, Instructions for Use (2.2)	01/2014
Warnings and Precautions, Immediate Post-Injection Reaction (5.1)	01/2014
Warnings and Precautions, Chest Pain (5.2)	01/2014
Warnings and Precautions, Lipoatrophy and Skin Necrosis (5.3)	01/2014

INDICATIONS AND USAGE

Glatopa™ is indicated for the treatment of patients with relapsing-forms of multiple sclerosis (1).

DOSAGE AND ADMINISTRATION

- For subcutaneous injection only; Glatopa 20 mg per mL dose is not interchangeable with glatramer acetate 40 mg per mL dose (2.1)
- Pediatric Use: The safety and effectiveness of Glatopa 20 mg/mL per day (2.1)
- Before use, allow the solution to warm to room temperature (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 20 mg/mL in a single-dose prefilled syringe with a white plunger (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

- INDICATIONS AND USAGE
- DOSAGE AND ADMINISTRATION
- DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS
- WARNINGS AND PRECAUTIONS
- ADVERSE REACTIONS
- DRUG INTERACTIONS

CONTRAINDICATIONS

Known hypersensitivity to glatramer acetate or mannitol (4)

WARNINGS AND PRECAUTIONS

- Immediate Post-Injection Reaction (flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and/or urticaria), generally transient and self-limiting (5.1)
- Chest pain, usually transient (5.2)
- Lipoatrophy and skin necrosis may occur. Instruct patients in proper injection technique and to rotate injection sites (5.3)
- Glatopa can modify immune response (5.4)

ADVERSE REACTIONS

- In controlled studies of glatramer acetate injection 20 mg/mL, most common adverse reactions (>10% and >1.5 times higher than placebo) were: injection site reactions, vasodilatation, rash, dyspnea, and chest pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: It is not known if glatramer acetate injection is excreted in human milk (8.3)
- Pediatric Use: The safety and effectiveness of Glatopa have not been established in patients under 18 years of age (8.4)

PATIENT COUNSELING INFORMATION

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2014

8 USE IN SPECIFIC POPULATIONS

8.1	Pregnancy
8.2	Labor and Delivery
8.3	Nursing Mothers
8.4	Pediatric Use
8.5	Geriatric Use
8.6	Use in Patients with Impaired Renal Function

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed

Table 1: Adverse reactions in controlled clinical trials with an incidence ≥2% of patients and more frequent with glatramer acetate injection (20 mg per mL daily) than with placebo

	Glatramer Acetate Injection 20 mg/mL (n=563)	Placebo (n=564)
Blood And Lymphatic System Disorders	Lymphadenopathy 7%	3%
Cardiac Disorders	Palpitations 9%	4%
	Tachycardia 5%	2%
Eye Disorders	Eye Disorder 3%	1%
	Diplopia 3%	2%
Gastrointestinal Disorders	Nausea 15%	11%
	Vomiting 7%	4%
	Dysphagia 2%	1%
General Disorders And Administration Site Conditions	Injection Site Erythema 43%	10%
	Injection Site Pain 40%	20%
	Injection Site Pruritus 27%	4%
	Injection Site Mass 26%	6%
	Asthenia 22%	21%
	Pain 20%	17%
	Injection Site Edema 19%	4%
	Chest Pain 13%	6%
	Injection Site Inflammation 9%	1%
	Edema 8%	2%
	Injection Site Reaction 8%	1%
	Pyrexia 6%	5%
	Injection Site Hypersensitivity 4%	0%
	Local Reaction 3%	1%
	Chills 3%	1%
	Face Edema 3%	1%
	Edema Peripheral 3%	2%
	Injection Site Fibrosis 2%	1%
	Injection Site Atrophy* 2%	0%
Immune System Disorders	Hypersensitivity 3%	2%
Infections And Infestations	Infection 30%	28%
	Influenza 14%	13%
	Rhinitis 7%	5%
	Bronchitis 6%	5%
	Gastroenteritis 6%	4%
	Vaginal Candidiasis 4%	2%
Metabolism And Nutrition Disorders	Weight Increased 3%	1%
Musculoskeletal And Connective Tissue Disorders	Back Pain 12%	10%
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)	Benign Neoplasm of Skin 2%	1%
Nervous System Disorders	Tremor 4%	2%
	Migraine 4%	2%
	Syncope 3%	2%
	Speech Disorder 2%	1%
	Anxiety 13%	10%
	Nervousness 2%	1%
	Micturition Urgency 5%	4%
	Dyspnea 14%	4%
	Cough 6%	5%
	Laryngospasm 2%	1%
Skin And Subcutaneous Tissue Disorders	Rash 19%	11%
	Hyperhidrosis 7%	5%
	Pruritus 5%	4%
	Urticaria 3%	1%
	Skin Disorder 3%	1%
Vascular Disorders	Vasodilatation 20%	5%

* Injection site atrophy comprises terms relating to localized lipoatrophy at injection site

Adverse reactions which occurred only in 4 to 5 more subjects in the glatramer acetate injection group than in the placebo group (less than 1% difference), but for which a relationship to glatramer acetate injection could not be excluded, were arthralgia and herpes simplex.

Laboratory analyses were performed on all patients participating in the clinical program for glatramer acetate injection. Clinically-significant laboratory values for hematology, chemistry, and urinalysis were similar for both glatramer acetate injection and placebo groups in blinded clinical trials. In controlled trials one patient discontinued treatment due to thrombocytopenia (16 x10⁹/L), which resolved after discontinuation of treatment.

Data on adverse reactions occurring in the controlled clinical trials of glatramer acetate injection 20 mg per mL were analyzed to evaluate differences based on sex. No clinically-significant differences were identified. Ninety-six percent of patients in these clinical trials were Caucasian. The majority of patients treated with glatramer acetate injection were between the ages of 18 and 45. Consequently, data are inadequate to perform an analysis of the adverse reaction incidence related to clinically-relevant age subgroups.

Other Adverse Reactions

In the paragraphs that follow, the frequencies of less commonly reported adverse clinical reactions are presented. Because the reports include reactions observed in open and uncontrolled premarketing studies (n=979), the role of glatramer acetate injection in their causation cannot be reliably determined. Furthermore, variability associated with adverse reaction reporting, the terminology used to describe adverse reactions, etc., limit the value of the quantitative frequency estimates provided. Reaction frequencies are calculated as the number of patients who used glatramer acetate injection and reported a reaction divided by the total number of patients exposed to glatramer acetate injection. All reported reactions are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse reactions are defined as those occurring in at least 1/100 patients and *Infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients.

Body as a Whole:
Frequent: Abscess
Infrequent: Injection site hematoma, moon face, cellulitis, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma, and photosensitivity reaction.
Cardiovascular:
Frequent: Hypertension
Infrequent: Hypotension, mid systolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension, and varicose veins.

Digestive:

Infrequent: Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discoloration, and duodenal ulcer.

Endocrine:

Infrequent: Goiter, hyperthyroidism, and hypothyroidism.

Gastrointestinal:

Frequent: Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis.

Hemic and Lymphatic:

Infrequent: Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly.

Metabolic and Nutritional:

Infrequent: Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma.

Musculoskeletal:

Infrequent: Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis.

Nervous:

Frequent: Abnormal dreams, emotional lability, and stupor.

Infrequent: Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, male reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression, and transient stupor.

Respiratory:

Frequent: Hyperventilation and hay fever.

Infrequent: Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration.

Skin and Appendages:

Frequent: Eczema, herpes zoster, pustular rash, skin atrophy, and warts.

Infrequent: Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash.

Special Senses:

Frequent: Visual field defect.

Infrequent: Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss.

Urogenital:

Frequent: Amenorrhea, hematuria, impotence, menorrhagia, suspicious papanicolaou smear, urinary frequency, and vaginal hemorrhage.

Infrequent: Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, carcinoma *in situ* cervix, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

6.2 Postmarketing Experience

The following adverse events occurring under treatment with glatramer acetate injection 20 mg per mL since market introduction and not mentioned above have been identified during postapproval use of glatramer acetate injection. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; allergic reaction; anaphylactoid reaction

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasic convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung

Special Senses: glaucoma; blindness

Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

7 DRUG INTERACTIONS

Interactions between glatramer acetate injection and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of glatramer acetate injection with therapies commonly used in MS patients, including the concurrent use of corticosteroids for up to 28 days. Glatramer acetate injection has not been formally evaluated in combination with interferon beta.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Administration of glatramer acetate by subcutaneous injection to pregnant rats and rabbits resulted in no adverse effects on offspring development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Glatopa should be used during pregnancy only if clearly needed.

In rats or rabbits receiving glatramer acetate by subcutaneous injection during the period of organogenesis, no adverse effects on embryo-fetal development were observed at doses up to 37.5 mg/kg/day (18 and 36 times, respectively, the therapeutic human dose of 20 mg/day on a mg/m² basis). In rats receiving subcutaneous glatramer acetate at doses of up to 36 mg/kg from day 15 of pregnancy throughout lactation, no significant effects on delivery or on offspring growth and development were observed.

8.2 Labor and Delivery

The effects of Glatopa on labor and delivery in pregnant women are unknown.

8.3 Nursing Mothers

It is not known if glatramer acetate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Glatopa is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of Glatopa have not been established in patients under 18 years of age.

8.5 Geriatric Use

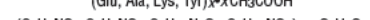
Glatopa has not been studied in elderly patients.

8.6 Use in Patients with Impaired Renal Function

The pharmacokinetics of glatramer acetate in patients with impaired renal function have not been determined.

11 DESCRIPTION

Glatramer acetate, the active ingredient of Glatopa, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatramer acetate is 5,000 – 9,000 daltons. Glatramer acetate is identified by specific antibodies. Chemically, glatramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:



CAS - 147245-92-9

Glatopa is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of glatramer acetate solution contains 20 mg of glatramer acetate and the following inactive ingredient, 40 mg of mannitol. The pH of the solution is approximately 5.5 to 7.0. The biological activity of glatramer acetate is determined by its ability to block the induction of experimental autoimmune encephalomyelitis (EAE) in mice.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism(s) by which glatramer acetate exerts its effects in patients with MS are not fully understood. However, glatramer acetate is thought to act by modifying immune processes that are believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental autoimmune encephalomyelitis, a condition induced in animals through immunization against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and *in vitro* systems suggest that upon its administration, glatramer acetate-specific suppressor T-cells are induced and activated in the periphery.

Because glatramer acetate can modify immune functions, concerns exist about its potential to alter naturally-occurring immune responses. There is no evidence that glatramer acetate does this, but this has not been systematically evaluated [see Warnings and Precautions (5.4)].

12.3 Pharmacokinetics

Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Larger fragments of glatramer acetate can be recognized by glatramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, mice were administered up to 60 mg/kg/day glatramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose of 20 mg/day on a mg/m² basis). No increase in systemic neoplasms was observed. In males receiving the 60-mg/kg/day dose, there was an increased incidence of fibrosarcomas at the injection sites. These sarcomas were associated with skin damage precipitated by repetitive injections of an irritant over a limited skin area.

In a 2-year carcinogenicity study, rats were administered up to 30 mg/kg/day glatramer acetate by subcutaneous injection (up to 15 times the human therapeutic dose on a mg/m² basis). No increase in neoplasms was observed.

Glatramer acetate was not mutagenic in *in vitro* (Ames test, mouse lymphoma tk) assays. Glatramer acetate was clastogenic in two separate *in vitro* chromosomal aberration assays in cultured human lymphocytes but not clastogenic in an *in vivo* mouse bone marrow micronucleus assay.

When glatramer acetate was administered by subcutaneous injection prior to and during mating (males and females) and throughout gestation and lactation (females) at doses up to 36 mg/kg/day (18 times the human therapeutic dose on a mg/m² basis) no adverse effects were observed on reproductive or developmental parameters.

The following adverse events occurring under treatment with glatramer acetate injection 20 mg per mL since market introduction and not mentioned above have been identified during postapproval use of glatramer acetate injection. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: sepsis; SLE syndrome; hydrocephalus; enlarged abdomen; allergic reaction; anaphylactoid reaction

Cardiovascular System: thrombosis; peripheral vascular disease; pericardial effusion; myocardial infarct; deep thrombophlebitis; coronary occlusion; congestive heart failure; cardiomyopathy; cardiomegaly; arrhythmia; angina pectoris

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

Musculoskeletal System: rheumatoid arthritis; generalized spasm

Nervous System: myelitis; meningitis; CNS neoplasm; cerebrovascular accident; brain edema; abnormal dreams; aphasic convulsion; neuralgia

Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung

Special Senses: glaucoma; blindness

Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

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Respiratory System: pulmonary embolus; pleural effusion; carcinoma of lung

Special Senses: glaucoma; blindness

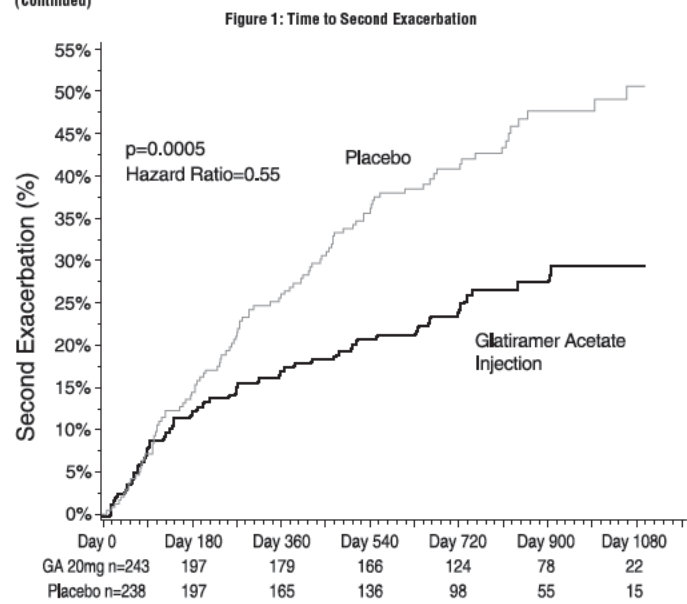
Urogenital System: urogenital neoplasm; urine abnormality; ovarian carcinoma; nephrosis; kidney failure; breast carcinoma; bladder carcinoma; urinary frequency

Digestive System: tongue edema; stomach ulcer; hemorrhage; liver function abnormality; liver damage; hepatitis; eructation; cirrhosis of the liver; cholelithiasis

Hemic and Lymphatic System: thrombocytopenia; lymphoma-like reaction; acute leukemia

Metabolic and Nutritional Disorders: hypercholesterolemia

(Continued)



Patients treated with glatiramer acetate injection demonstrated fewer new T2 lesions at the last observation (rate ratio 0.41; confidence interval 0.28 to 0.59; $p < 0.0001$). Additionally, baseline-adjusted T2 lesion volume at the last observation was lower for patients treated with glatiramer acetate injection (ratio of 0.89; confidence interval 0.84 to 0.94; $p = 0.0001$).

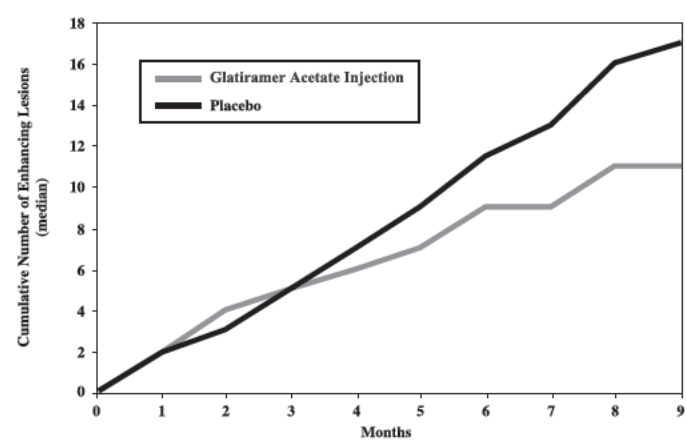
Study 4 was a multinational study in which MRI parameters were used both as primary and secondary endpoints. A total of 239 patients with RMS (glatiramer acetate injection: $n=119$; and placebo: $n=120$) were randomized. Inclusion criteria were similar to those in the second study with the additional criterion that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over the nine months. Table 4 summarizes the results for the primary outcome measure monitored during the trial for the intent-to-treat cohort.

Table 4: Study 4 MRI Results

	Glatiramer Acetate Injection 20 mg/mL (n=119)	Placebo (n=120)	P-Value
Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	11	17	0.0030

Figure 2 displays the results of the primary outcome on a monthly basis.

Figure 2: Median Cumulative Number of Gd-Enhancing Lesions



16 HOW SUPPLIED/STORAGE AND HANDLING

Glatopa (glatiramer acetate injection) is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution in a 1 mL single-dose glass syringe with attached 1/2 inch length and 29 gauge needle supplied as:

- 20 mg per mL in a single-dose, pre-filled syringe with a white plunger, in individual blister packages supplied in 30-count cartons with 34 alcohol wipes (NDC 0781-3234-34)
- Store Glatopa refrigerated at 2°C to 8°C (36°F to 46°F). If needed, the patient may store Glatopa at room temperature, 15°C to 30°C (59°F to 86°F), for up to one month, but refrigeration is preferred. Avoid exposure to higher temperatures or intense light. Do not freeze Glatopa. If a Glatopa syringe freezes, it should be discarded.

17 PATIENT COUNSELING INFORMATION

[See Patient Information Leaflet (Patient Information and Instructions for Use)]
 Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy
 Instruct patients that if they are pregnant or plan to become pregnant while taking Glatopa they should inform their physician.

Immediate Post-Injection Reaction
 Advise patients that Glatopa may cause various symptoms after injection, including flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat, and urticaria. These symptoms are generally transient and self-limited and do not require specific treatment. Inform patients that these symptoms may occur early or may have their onset several months after the initiation of treatment. A patient may experience one or several episodes of these symptoms.

Chest Pain

Advise patients that they may experience transient chest pain either as part of the immediate Post-injection Reaction or in isolation. Inform patients that the pain should be transient. Some patients may experience more than one such episode, usually beginning at least one month after the initiation of treatment. Patients should be advised to seek medical attention if they experience chest pain of unusual duration or intensity.

Lipoatrophy and Skin Necrosis at Injection Site
 Advise patients that localized lipoatrophy, and rarely, skin necrosis may occur at injection sites. Instruct patients to follow proper injection technique and to rotate injection areas and sites with each injection to minimize these risks.

Instructions for Use
 Instruct patients to read the Glatopa Patient Information leaflet carefully. Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable. Glatiramer acetate injection 20 mg per mL is administered daily. Caution patients to use aseptic technique. The first injection should be performed under the supervision of a health care professional. Instruct patients to rotate injection areas and sites with each injection. Caution patients against the reuse of needles or syringes. Instruct patients in safe disposal procedures.

Storage Conditions
 Advise patients that the recommended storage condition for Glatopa is refrigeration at 36°F to 46°F (2°C to 8°C). If needed, the patient may store Glatopa at room temperature, 59°F to 86°F (15°C to 30°C), for up to one month, but refrigeration is preferred. Glatopa should not be exposed to higher temperatures or intense light. Do not freeze Glatopa.

PATIENT INFORMATION Glatopa™ (Glatiramer Acetate Injection) for Subcutaneous Use

Read this Patient Information before you start using Glatopa and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is Glatopa?

Glatopa is prescription medicine used for the treatment of people with relapsing forms of multiple sclerosis (MS). It is not known if Glatopa is safe and effective in children under 18 years of age. Glatopa is supplied as a 1 mL single dose glass syringe with attached 1/2 inch length and 29 gauge needle.

Who should not use Glatopa?
 • Do not use Glatopa if you are allergic to glatiramer acetate or mannitol.

What should I tell my doctor before using Glatopa? Before you use Glatopa, tell your doctor if you:
 • are pregnant or plan to become pregnant. It is not known if glatiramer acetate will harm your unborn baby.
 • are breastfeeding or plan to breastfeed. It is not known if glatiramer acetate passes into your breast milk.
 • Talk to your doctor about the best way to feed your baby while using Glatopa.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Glatopa may affect the way other medicines work, and other medicines may affect how glatiramer acetate works.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I use Glatopa?
 • For detailed instructions, see the Instructions for Use at the end of this leaflet for complete information on how to use Glatopa.

Your doctor will tell you how much Glatopa to use and when to use it.
 • Glatopa is given by injection under your skin (subcutaneously).
 • Use Glatopa exactly as your doctor tells you to use it.
 • Since every body type is different, talk with your doctor about the injection areas that are best for you.
 • You should receive your first dose of Glatopa with a doctor or nurse present. This might be at your doctor's office or with a visiting home health nurse who will teach you how to give your Glatopa injections.

What are the possible side effects of Glatopa?

Glatopa may cause serious side effects, including:
 • Post-injection Reactions. Serious side effects may happen right after you inject Glatopa at any time during your course of treatment. Call your doctor right away if you have any of these post-injection reaction symptoms including:

- redness to your cheeks or other parts of the body (flushing)
 - chest pain
 - fast heart beat
 - anxiety
 - breathing problems or tightness in your throat
 - swelling, rash, hives, or itching
- If you have symptoms of a post-injection reaction, do not give yourself more injections until a doctor tells you to.
- Chest Pain.** You can have chest pain as part of a post-injection reaction or by itself. This type of chest pain usually lasts a few minutes and can begin around 1 month after you start using Glatopa. Call your doctor right away if you have chest pain while using Glatopa.
- Damage to your skin.** Damage to the fatty tissue just under your skin's surface (lipoatrophy) and, rarely, death of your skin tissue (necrosis) can happen when you use Glatopa. Damage to the fatty tissue under your skin can cause a "dent" at the injection site that may not go away. You can reduce your chance of developing these problems by:
- following your doctor's instructions for how to use Glatopa
 - choosing a different injection area each time you use Glatopa.

See Step 4 in the Instructions for Use, "Choose your injection area".
 The most common side effects of Glatopa include:
 • skin problems at your injection site including:

- redness
- pain
- swelling
- itching
- lumps
- rash
- shortness of breath
- flushing (vasodilation)

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Glatopa. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Glatopa?

Store Glatopa in the refrigerator between 36°F to 46°F (2°C to 8°C).
 When you are not able to refrigerate Glatopa, you may store it for up to 1 month at room temperature between 59°F to 86°F (15°C to 30°C).
 Protect Glatopa from light or high temperature.
 Do not freeze Glatopa syringes. If a syringe freezes, throw it away in a sharps disposal container. See Step 13 in the Instructions for Use, "Dispose of needles and syringes".
 Keep Glatopa and all medicines out of the reach of children.

General Information about the safe and effective use of Glatopa.
 Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use Glatopa for a condition for which it was not prescribed. Do not give Glatopa to other people, even if they have the same symptoms as you have. It may harm them.

This Patient Information Leaflet summarizes the most important information about Glatopa. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Glatopa that is written for health professionals.

For more information, go to www.glatopa.com or call Sandoz Glatopa Care at 1-855-452-8672.

What are the ingredients in Glatopa?

Active ingredient: glatiramer acetate
Inactive ingredients: mannitol

INSTRUCTIONS FOR USE Glatopa™ (Glatiramer Acetate Injection) for Subcutaneous Use

For subcutaneous injection only. Do not inject Glatopa in your veins (intravenously). Do not re-use your Glatopa prefilled syringes. Do not share your Glatopa prefilled syringes with another person. You may give another person an infection or get an infection from them.

You should receive your first dose of Glatopa with a doctor or nurse present. This might be at your doctor's office or with a visiting home health nurse who will show you how to give your own injections. Glatopa comes in a 20 mg Prefilled Syringe with needle attached.

Instructions for Using Your Glatopa 20 mg Prefilled Syringe dose:

- Glatopa 20 mg is injected 1 time each day, in the fatty layer under your skin (subcutaneously).
- Each Glatopa 20 mg prefilled syringe is for single use (1 time use) only.
- The Glatopa 20 mg dose is packaged in boxes of 30 prefilled syringes with needles attached. Glatopa 20 mg prefilled syringes have white plungers.

How do I inject Glatopa?
Step 1: Gather the supplies you will need to inject Glatopa. See Figure A.

- 1 blister pack with a Glatopa prefilled syringe with needle attached
- Alcohol wipe
- Dry cotton ball (not supplied)
- A place to record your injections, like a notebook (not supplied)
- Sharps disposal container (not supplied). See Step 13 below, "Dispose of needles and syringes".

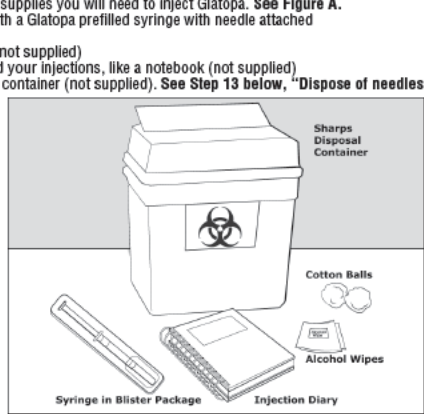


Figure A

Step 2: Remove only 1 blister pack from the Glatopa prefilled syringe carton. See Figure B.

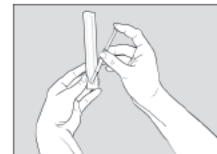


Figure B

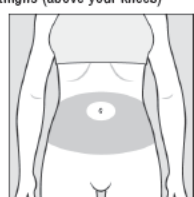
- Place the supplies you will need on a clean, flat surface in a well-lit area.
- After you remove 1 blister pack from the carton, keep all unused syringes in the carton and store them in the refrigerator.
- Let the blister pack, with the syringe inside, warm to room temperature for about 20 minutes.
- Wash your hands. Be careful not to touch your face or hair after washing your hands.

Step 3: Look closely at your Glatopa prefilled syringe. Do not try to push the air bubble from the syringe before giving your injection so you do not lose any medicine.

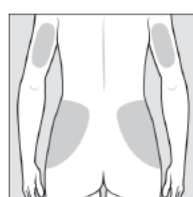
- There may be small air bubbles in the syringe. Do not try to push the air bubble from the syringe before giving your injection so you do not lose any medicine.
- Check the liquid medicine in the syringe before you give your injection. The liquid in the syringe should look clear, and colorless, and may look slightly yellow. If the liquid is cloudy or contains any particles, do not use the syringe and throw it away in a sharps disposal container. See Step 13 below, "Dispose of needles and syringes."

Step 4: Choose your injection area. See Figure C.
 See the injection areas you should use on your body. Talk with your doctor about the injection areas that are best for you.

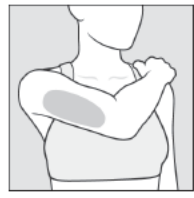
- The possible injection areas on your body include (See Figure C):
 - your stomach area (abdomen) around the belly button
 - the back of your upper arms
 - upper hips (below your waist)
 - your thighs (above your knees)



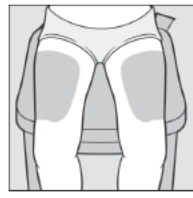
Abdomen Avoid about 2 inches around the belly button



Back of Hips and Arms Fleshy areas of the upper hips, always below the waist. Fleshy areas of the upper back portion of the arms



Arms Fleshy areas of the upper back portion



Thighs About 2 inches above the knee and 2 inches below the groin

Figure C

- For each Glatopa dose, choose a different injection area from 1 of the areas shown above. See Figure C.
- Do not stick the needle in the same place (site) more than 1 time each week. Each injection area contains multiple injection sites for you to choose from. Avoid injecting in the same site over and over again.
- Keep a record of the sites where you give your injection each day so you will remember where you already injected.

Step 5: Prepare to give your injection.
 • There are some injection areas on your body that are hard to reach (like the back of your arm). You may need help from someone who has been instructed on how to give your injection if you cannot reach certain injection areas.

- Do not inject in sites where the skin has scarring or "dents". Using scarred or dented skin for your injections may make your skin worse.

Step 6: Clean your injection site.
 • Clean the injection site using the alcohol wipe and allow your skin to air dry. See Figure D.



Figure D

Step 7: Pick up the syringe with 1 hand and hold it like a pencil. Remove the needle cover with your other hand and set it aside. See Figure E.

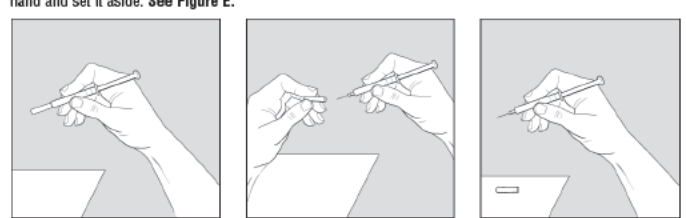


Figure E

Step 8: Pinch about a 2 inch fold of skin between your thumb and index finger. See Figure F.

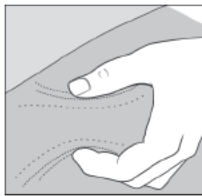


Figure F

Step 9: Giving your injection.
 • Rest the heel of your hand holding the syringe against your skin at the injection site. Insert the needle at a 90 degree angle straight into your skin. See Figure G.



Figure G

- When the needle is all the way into your skin, release the fold of skin. See Figure H.



Figure H

Step 10: Give your Glatopa injection.
 To inject the medicine, hold the syringe steady and slowly push down the plunger. See Figure I.

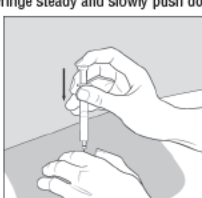


Figure I

Step 11: Remove the needle.
 After you have injected all of the medicine, pull the needle straight out. See Figure J.

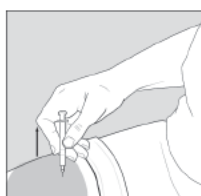


Figure J

Step 12: Use a clean, dry cotton ball to gently press on the injection site for a few seconds. Do not rub the injection site or re-use the needle or syringe. See Figure K.



Figure K

Step 13: Dispose of your needles and syringes.
 • Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) loose needles and syringes in your household trash.

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of a heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.



Figure L

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration. 03-2014M

Distributed by Sandoz Inc. Princeton, NJ 08540

NDC 0781 3234 71

GSYR 03

GlatopaTM
(glatiramer acetate injection)

Rx only

20 mg/mL

1 mL for one subcutaneous
injection only

 **SANDOZ**

04 2014M



(b) (4)

S

SANDOZ
a Novartis company

Contains 30 Single-Use PRE-FILLED Syringes
and 34 Alcohol Preps (Swabs)

Rx only

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light.
Retain in carton.

20 mg/mL For Subcutaneous
Injection Only

Glatopa™
(glatiramer acetate injection)

ONCE DAILY

NDC 0781-3234-34

NDC 0781-3234-34

ONCE DAILY
Glatopa™
(glatiramer acetate injection)

20 mg/mL For Subcutaneous
Injection Only

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light.
Retain in carton.

Rx only Contains 30 Single-Use PRE-FILLED Syringes
and 34 Alcohol Preps (Swabs)

SANDOZ
a Novartis company

S

Each pre-filled syringe contains: 1 mL solution of glatiramer acetate 20 mg
Inactive ingredient: mannitol 40 mg
Supplied as: 1 mL single dose glass syringe with attached 1/2 inch length and
29 gauge needle
Usual Dosage: See package insert.
Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. **Retain in carton.**
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Distributed By
Sandoz Inc., Princeton, NJ 08540 04-2014M

GCAR-03

NDC 0781-3234-34

ONCE DAILY
Glatopa™
(glatiramer acetate injection)

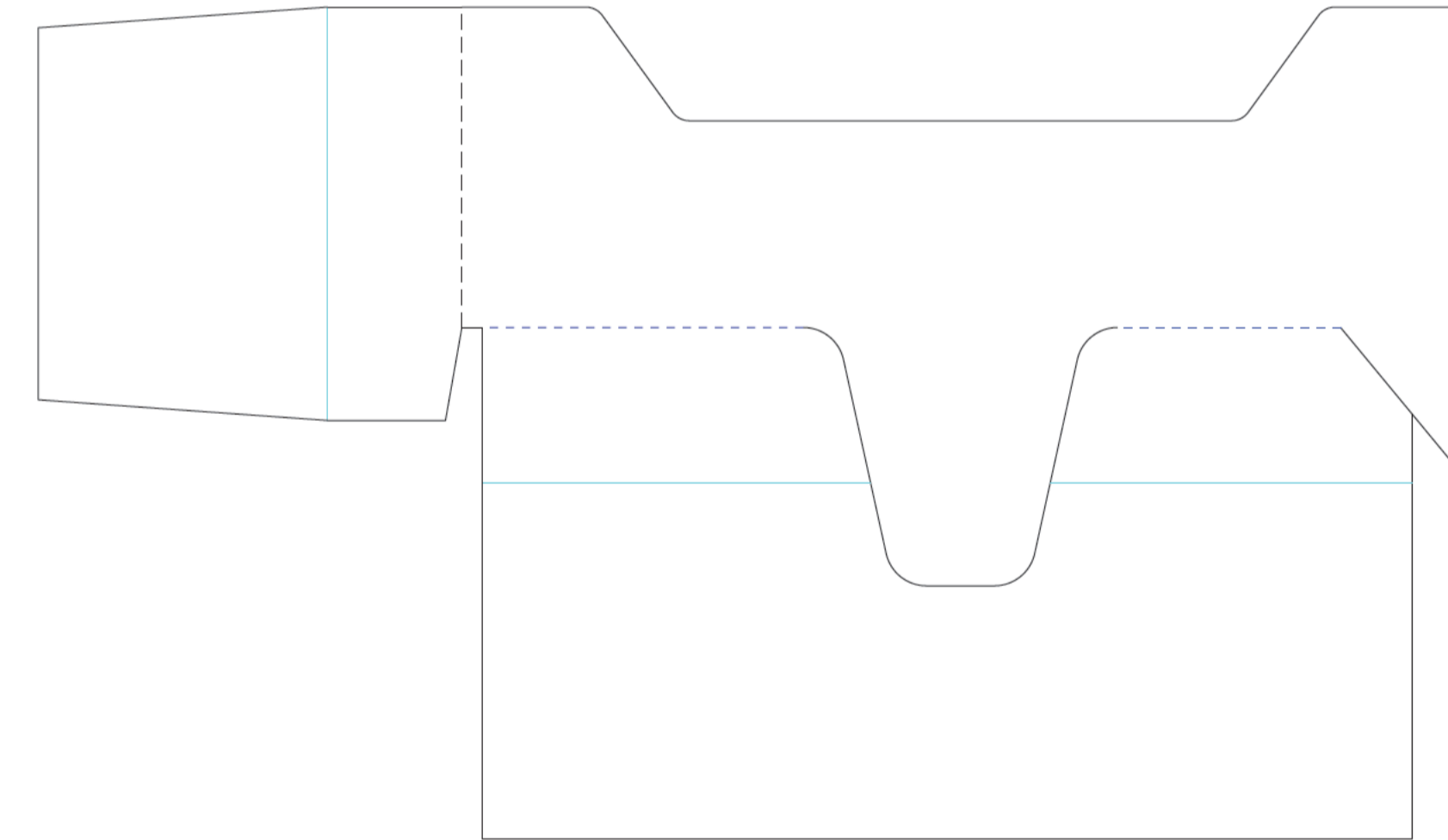
20 mg/mL For Subcutaneous
Injection Only

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light.
Retain in carton.

Rx only Contains 30 Single-Use PRE-FILLED Syringes
and 34 Alcohol Preps (Swabs)

SANDOZ
a Novartis company

S



NDC 0781-3234-71

Glatopa™ 20 mg/mL
(glatiramer acetate injection)

GLID-02

FOR SUBCUTANEOUS INJECTION ONLY

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient).

Distributed by Sandoz Inc., Princeton, NJ 08540

ONCE DAILY

03-2014M

 **SANDOZ**

R_x only



NDC 0781-3234-71

Glatopa™ 20 mg/mL
(glatiramer acetate injection)

GLID-02

FOR SUBCUTANEOUS INJECTION ONLY

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient).

Distributed by Sandoz Inc., Princeton, NJ 08540

ONCE DAILY

03-2014M

 **SANDOZ**

R_x only



NDC 0781-3234-71

Glatopa™ 20 mg/mL
(glatiramer acetate injection)

GLID-02

FOR SUBCUTANEOUS INJECTION ONLY

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient).

Distributed by Sandoz Inc., Princeton, NJ 08540

ONCE DAILY

03-2014M

 **SANDOZ**

R_x only



NDC 0781-3234-71

Glatopa™ 20 mg/mL
(glatiramer acetate injection)

GLID-02

FOR SUBCUTANEOUS INJECTION ONLY

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient).

Distributed by Sandoz Inc., Princeton, NJ 08540

ONCE DAILY

03-2014M

 **SANDOZ**

R_x only



NDC 0781-3234-71

Glatopa™ 20 mg/mL
(glatiramer acetate injection)

GLID-02

FOR SUBCUTANEOUS INJECTION ONLY

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient).

Distributed by Sandoz Inc., Princeton, NJ 08540

ONCE DAILY

03-2014M

 **SANDOZ**

R_x only



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 090218

LABELING REVIEWS

Office of Generic Drugs

LABELING APPROVAL SUMMARY REVIEW OF PROFESSIONAL LABELING (#4 Cycle)

ANDA Number: 090218
Dates of Submissions: March 26 and April 3, 2014
Applicant: Sandoz, Inc.
Established Name and Strength: Glatiramer Acetate Injection, 20 mg/mL, 1 mL prefilled syringe
Proposed Proprietary Name: Glatopa

Labeling Comments below are considered:

- Minor Deficiency *
* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.
- No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

The Labeling Review Branch has no further questions/comments at this time based on your labeling submissions dated March 26 and April 3, 2014.

Please continue to monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book and the NF-USP online for recent updates, and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL?

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER	4/3/2014	Final	Acceptable
CARTON	4/3/2014	Final	Acceptable
BLISTER	3/26/2014	Final	Acceptable
INSERT	3/26/2014	Final	Acceptable
PATIENT INFORMATION and INSTRUCTIONS FOR USE	3/26/2014	Final	Acceptable
SPL	3/26/2014		Acceptable

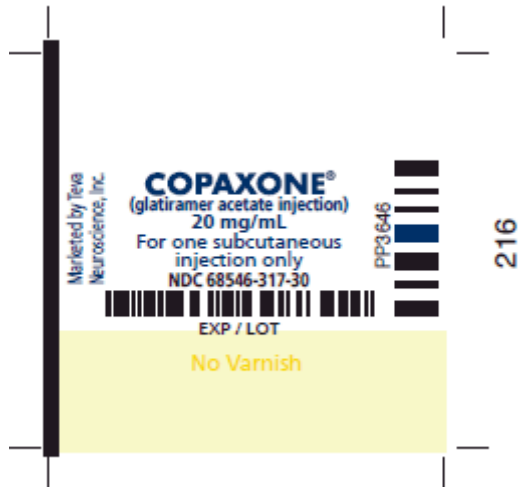
FOR THE RECORD:

1. MODEL LABELING

Labeling based on RLD, Teva's Copaxone (NDA 20-622/S-089 approved 1/28/2014). S-089 provides for a new dosing strength of 40 mg/mL administered three times per week.

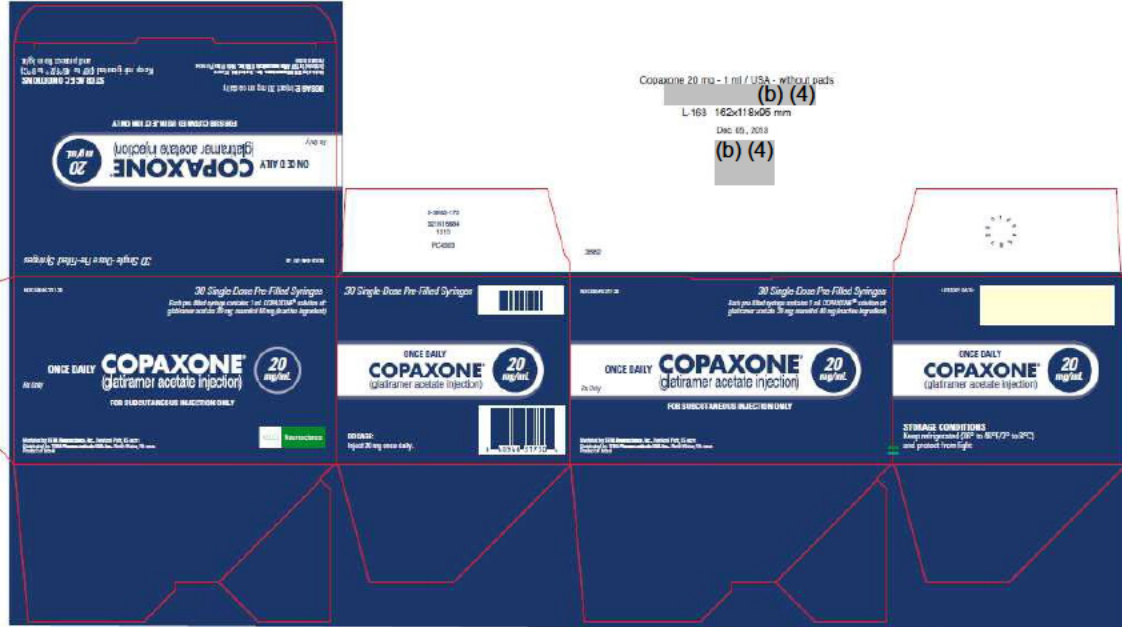
S-087 provides for removal of the alcohol preps (swabs) from the Copaxone kit.

20 mg Copaxone labels

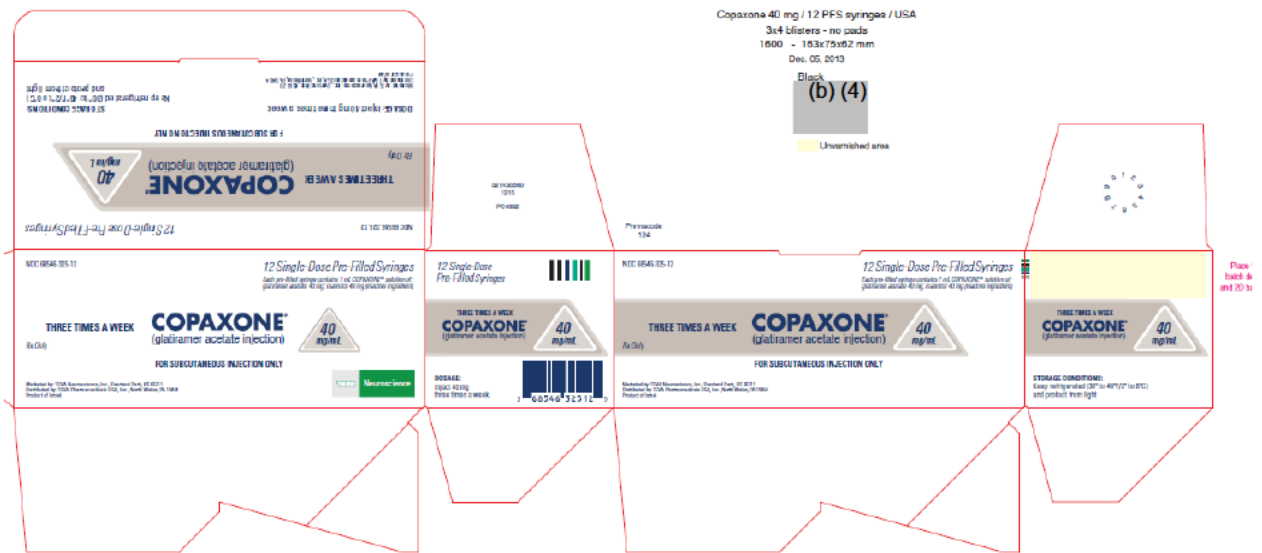


3-3942-172





40 mg Copaxone Labels



LOT xxxxxx
EXP mm/yyyy

COPAXONE®
(glatiramer acetate injection)

Rx only
Marketed by: TEVA Neuroscience, Inc.,
Overland Park, KS 66211

40 mg/mL

FOR SUBCUTANEOUS INJECTION ONLY
THREE TIMES A WEEK

NDC 68546-325-12

Each pre-filled syringe contains 1 mL COPAXONE® solution of:
glatiramer acetate 40 mg; mannitol 40 mg (inactive ingredient)
Storage conditions: keep refrigerated (36° to 46°F/2° to 8°C) and protect from light

LOT xxxxxx
EXP mm/yyyy

COPAXONE®
(glatiramer acetate injection)

Rx only
Marketed by: TEVA Neuroscience, Inc.,
Overland Park, KS 66211

40 mg/mL

FOR SUBCUTANEOUS INJECTION ONLY
THREE TIMES A WEEK

NDC 68546-325-12

Each pre-filled syringe contains 1 mL COPAXONE® solution of:
glatiramer acetate 40 mg; mannitol 40 mg (inactive ingredient)
Storage conditions: keep refrigerated (36° to 46°F/2° to 8°C) and protect from light

LOT xxxxxx
EXP mm/yyyy

COPAXONE®
(glatiramer acetate injection)

Rx only
Marketed by: TEVA Neuroscience, Inc.,
Overland Park, KS 66211

40 mg/mL

FOR SUBCUTANEOUS INJECTION ONLY
THREE TIMES A WEEK

NDC 68546-325-12

Each pre-filled syringe contains 1 mL COPAXONE® solution of:
glatiramer acetate 40 mg; mannitol 40 mg (inactive ingredient)
Storage conditions: keep refrigerated (36° to 46°F/2° to 8°C) and protect from light

LOT xxxxxx
EXP mm/yyyy

COPAXONE®
(glatiramer acetate injection)

Rx only
Marketed by: TEVA Neuroscience, Inc.,
Overland Park, KS 66211

40 mg/mL

FOR SUBCUTANEOUS INJECTION ONLY
THREE TIMES A WEEK

NDC 68546-325-12

Each pre-filled syringe contains 1 mL COPAXONE® solution of:
glatiramer acetate 40 mg; mannitol 40 mg (inactive ingredient)
Storage conditions: keep refrigerated (36° to 46°F/2° to 8°C) and protect from light

LOT xxxxxx
EXP mm/yyyy

COPAXONE®
(glatiramer acetate injection)

Rx only
Marketed by: TEVA Neuroscience, Inc.,
Overland Park, KS 66211

40 mg/mL

FOR SUBCUTANEOUS INJECTION ONLY
THREE TIMES A WEEK

NDC 68546-325-12

Each pre-filled syringe contains 1 mL COPAXONE® solution of:
glatiramer acetate 40 mg; mannitol 40 mg (inactive ingredient)
Storage conditions: keep refrigerated (36° to 46°F/2° to 8°C) and protect from light

LOT xxxxxx
EXP mm/yyyy

COPAXONE®
(glatiramer acetate injection)

Rx only
Marketed by: TEVA Neuroscience, Inc.,
Overland Park, KS 66211

40 mg/mL

FOR SUBCUTANEOUS INJECTION ONLY
THREE TIMES A WEEK

NDC 68546-325-12

Each pre-filled syringe contains 1 mL COPAXONE® solution of:
glatiramer acetate 40 mg; mannitol 40 mg (inactive ingredient)
Storage conditions: keep refrigerated (36° to 46°F/2° to 8°C) and protect from light

LOT xxxxxx
EXP mm/yyyy

COPAXONE®
(glatiramer acetate injection)

Rx only
Marketed by: TEVA Neuroscience, Inc.,
Overland Park, KS 66211

**20mg
1mL**

NDC 68546-317-30

FOR SUBCUTANEOUS INJECTION ONLY
ONCE DAILY

Each pre-filled syringe contains 1 mL COPAXONE® solution of:
glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient)
Storage conditions: keep refrigerated (36° to 46°F/2° to 8°C) and protected from light

Copaxone® (glatiramer acetate injection) 20 mg/1 mL Syringe Blister Text

**COPAXONE®
(glatiramer acetate injection)**

MedWatch – no reference found [checked on April 7, 2014]

2. **USP & PF** [Checked on April 7, 2014] DS and DP are non compendial
3. **PATENT AND EXCLUSIVITY** [Checked on April 7, 2014]

Patent Data – 20622

No	Expiration	Use Code	Use	How filed	Labeling Impact
5981589	May 24, 2014			IV	None
6054430	May 24, 2014			IV	None
6342476	May 24, 2014	U-441	Method of treating MS by administering Copaxone	IV	None
6362161	May 24, 2014	U-441	Method of treating MS by administering Copaxone	IV	None
6620847	May 24, 2014			IV	None

6939539	May 24, 2014			IV	None
7199098	May 24, 2014			IV	None
8367605	May 24, 2014			IV	None

No unexpired exclusivity

Patent amendment dated 11/22/2013: Sandoz and Mylan lost on appeal and court decided that generic companies infringed on the patents. Thus, Sandoz and Mylan could not market until expiration of patents.

4. **INACTIVE INGREDIENTS** [Chem Review #3]

Each 1 mL of glatiramer acetate solution contains 20 mg of glatiramer acetate and the following inactive ingredient 40 mg of mannitol. The pH of the solution is approximately 5.5 to 7.0 [PI]

[Chem Review #3] Glatiramer Acetate Injection 20 mg/mL is a clear, colorless to slightly yellow solution of pH ~ 6.9 composed of glatiramer acetate 20 mg and mannitol 40 mg dissolved in water for injection.

Glatiramer acetate is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio.

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide).

Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification.

The major challenge or high risk area is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.

5. **MANUFACTURING FACILITY** [Chem Review #3]

(b) (4)

6. **FINISHED PRODUCT DESCRIPTION AND PRODUCT LINE**

RLD: COPAXONE (glatiramer acetate injection) is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution supplied as:

- 20 mg per mL in a single-dose, prefilled syringe with a white plunger, in individual blister packages supplied in 30-count cartons (NDC 68546-317-30).
- 40 mg per mL in a single-dose, prefilled syringe with a blue plunger, in individual blister packages supplied in 12-count cartons (NDC 68546-325-12).

ANDA: Glatopa (glatiramer acetate injection) is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution in a 1 mL single-dose glass syringe with attached 1/2 inch length and 29 gauge needle supplied as:

- 20 mg per mL in a single-dose, prefilled syringe with a white plunger, in individual blister

packages supplied in 30-count cartons with 34 alcohol preps (NDC 0781-3234-34)

7. STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS

RLD: Store COPAXONE refrigerated at 2°C to 8°C (36°F to 46°F). If needed, the patient may store COPAXONE at room temperature, 15°C to 30°C (59°F to 86°F), for up to one month, but refrigeration is preferred. Avoid exposure to higher temperatures or intense light. Do not freeze COPAXONE. If a COPAXONE syringe freezes, it should be discarded.

ANDA: Store Glatopa refrigerated at 2°C to 8°C (36°F to 46°F). If needed, the patient may store Glatopa at room temperature, 15°C to 30°C (59°F to 86°F), for up to one month, but refrigeration is preferred. Avoid exposure to higher temperatures or intense light. Do not freeze Glatopa. If a Glatopa syringe freezes, it should be discarded.

8. CONTAINER/CLOSURE [Chem Review #2]

3.2.P.7.1 Summary of Packaging System

The primary packaging components consist of a Type 1 glass syringe with a fixed needle and rigid needle shield and a stopper. A plunger rod is applied to the stopper. Details of each component are given in Table 1.

Table 1. Description of Primary Packaging Components

Component	Description	Supplier	DMF
Syringe barrel	Type 1 clear glass barrel with 29 Ga ½ inch fixed needle and (b) (4) rigid needle shield	[REDACTED]	(b) (4)
Stopper	(b) (4) Gray (b) (4)		
Plunger rod	Clear (b) (4)		

9. PATIENT PACKAGE INSERT and INSTRUCTION FOR USE

In 3/26/2014 submission: **Sandoz Comment:** Sandoz intends to package the 30 syringes, wipes, and labeling components including the patient information and instruction for use in one carton to be dispensed to the patient.

10. RELATED APPLICATIONS- [REDACTED] (b) (4)

11. SPL DATA ELEMENTS

DLDE acceptable in 3/26/2014 submission.

12. CITIZENS PETITION: Yes, Teva submitted CP claiming that generic products are NOT bio-equivalent. The CP is pending with the Agency and the expected response is due on 5/4/2014.

PROPRIETARY NAME: DMEPA found the proprietary name “Glatopa” for Sandoz’s product acceptable (see proprietary name letter dated 1/17/2013).

Via an email dated 4/11/2014: DMEPA confirmed that they will not need to re-review the trade name Glatopa.

Sandoz’s **3/4/2014 withdrawal submission** pertains to the 1/19/2014 proprietary name logo.

(b) (4)
Sandoz proposed (b) (4) in the 1/19/2014 submission and in the 12/11/2013 labeling submission.

I did not review the 12/11/2013 submission b/c Sandoz withdrew the submission per the 3/4/2014 communication.

(b) (4)
In the labeling submission, 2/12/2014, Sandoz proposed (b) (4).

3/26/2014: Sandoz submitted physical sample on 3/26/2014 with the (b) (4) background color. I could see the container label clearly on syringe.

4/2/2014: Sandoz submitted revised the carton and syringe labeling from a (b) (4) colored background to a lime background color on 4/3/2014. The blister label remained the same.



→

13. LABELING STATEMENT “ 40 mg/mL are not interchangeable”

OND recently approved the 40 mg/mL strength for the RLD. The new strength, 40 mg/mL will receive exclusivity (see exclusivity summary dated 1/28/2014). Currently, the exclusivity is NOT posted on the OB. Because of the imminent RLD 40 mg strength exclusivity, the generic labeling will NOT include reference to the 40 mg strength. However, due to safety concerns, “COPAXONE 20 mg per mL and COPAXONE 40 mg per mL are not interchangeable” will be in the Sandoz’s labeling as “Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable”. The phrase will in the Sandoz’s labeling under these subsections: the HIGHLIGHTS, DOSAGE and ADMINISTRATION; 2.1 Recommended dose; and 17 PATIENT COUNSELING INFORMATION.

14. ANDA LABELS



Syringe Label

NDC 0781-3234-71 G5YR-03

Glatopa™
(glatiramer acetate injection) **Rx only**

20 mg/mL 1 mL for one subcutaneous injection only

SANDOZ 04-2014M

Blister Lidding

NDC 0781-3234-71


Glatopa™ **20 mg/mL**
(glatiramer acetate injection)

GLID-02

FOR SUBCUTANEOUS INJECTION ONLY
Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient). Distributed by Sandoz Inc., Princeton, NJ 08540

ONCE DAILY
03-2014M

SANDOZ **Rx only**



NDC 0781-3234-71


Glatopa™ **20 mg/mL**
(glatiramer acetate injection)

GLID-02

FOR SUBCUTANEOUS INJECTION ONLY
Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient). Distributed by Sandoz Inc., Princeton, NJ 08540

ONCE DAILY
03-2014M

SANDOZ **Rx only**



NDC 0781-3234-71


Glatopa™ **20 mg/mL**
(glatiramer acetate injection)

GLID-02

FOR SUBCUTANEOUS INJECTION ONLY
Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient). Distributed by Sandoz Inc., Princeton, NJ 08540

ONCE DAILY
03-2014M

SANDOZ **Rx only**



Carton label



(b) (4)

SANDOZ **Rx only**

Glatopa™ **20 mg/mL**
(glatiramer acetate injection)

ONCE DAILY

NDC 0781-3234-04

Glatopa™
(glatiramer acetate injection)
20 mg/mL For Subcutaneous Injection Only

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient). Distributed by Sandoz Inc., Princeton, NJ 08540

SANDOZ **Rx only**

SANDOZ **Rx only**

Glatopa™ **20 mg/mL**
(glatiramer acetate injection)

ONCE DAILY

NDC 0781-3234-04

Glatopa™
(glatiramer acetate injection)
20 mg/mL For Subcutaneous Injection Only

Keep refrigerated 2° to 8°C (36° to 46°F). Protect from light. Retain in carton. Each pre-filled syringe contains 1 mL solution of: glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient). Distributed by Sandoz Inc., Princeton, NJ 08540

SANDOZ **Rx only**

SANDOZ **Rx only**

Date of Review: April 7, 2014

Primary Reviewer: Thuyanh Vu

Team Leader: Malik Imam

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
04/11/2014

MALIK M IMAM
04/14/2014

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING (#3 Cycle)

ANDA Number:	090218
Dates of Submissions:	December 11, 2013 and February 12, 2014
Applicant:	Sandoz, Inc.
Established Name and Strength:	Glatiramer Acetate Injection, 20 mg/mL, 1 mL prefilled syringe
Proposed Proprietary Name:	Glatopa

Labeling Comments below are considered:

Minor Deficiency *

* Please note that the RPM may change the status from Minor Deficiency to Easily Correctable Deficiency if other disciplines are acceptable.

No Comments (Labeling Approval Summary or Tentative Approval Summary)

RPM Note - Labeling comments to be sent to the firm start below:

Labeling Deficiencies determined on March 12, 2014, based on your submission dated February 12, 2014:

1. CONTAINER

Please submit syringe samples and ensure that the labels could be easily read.

2. BLISTER

Add directly above the "Keep refrigerated ..." statement,

"FOR SUBCUTANEOUS INJECTION ONLY

ONCE DAILY"

If space is at a premium, you may delete the needle information, "Supplied as 1 mL single dose..."

Refer to the Reference Listed Drug's labeling for guidance.

3. CARTON

Add "ONCE DAILY" to appear directly above "Glatopa". "ONCE DAILY" should be the same type size as the established name "glatiramer acetate injection". Refer to the Reference Listed Drug's labeling for guidance.

4. PRESCRIBING INFORMATION/PHYSICIAN INSERT

- HIGHLIGHTS, DOSAGE AND ADMINISTRATION, first bullet, revise to state "For subcutaneous injection only, Glatopa 20 mg per mL dose is not interchangeable with glatiramer acetate 40 mg per mL dose.
- 2.1 Recommended Dose, add "Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable".
- 17 PATIENT COUNSELING INFORMATION, Instructions for Use, add the following as the second sentence in this subsection: "Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable."

5. PATIENT INFORMATION and INSTRUCTION FOR USE

What is your plan to ensure that each patient receives these labeling pieces upon dispensing?

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Note RPM - Labeling comments end here

REVISIONS NEEDED POST APPROVAL?

NOTES/QUESTIONS TO THE CHEMIST/BIO REVIEWER/MICRO REVIEWER:

Review Summary

Labeling Submitted	Date submitted	Final or Draft	Recommendation
CONTAINER	2/12/2014	Draft	Revise
CARTON	2/12/2014	Draft	Revise
BLISTER	2/12/2014	Draft	Revise
INSERT	2/12/2014	Draft	Revise
PATIENT INFORMATION and INSTRUCTIONS FOR USE	2/12/2014	Final	Acceptable
SPL	2/12/2014		Acceptable

REMS required? No

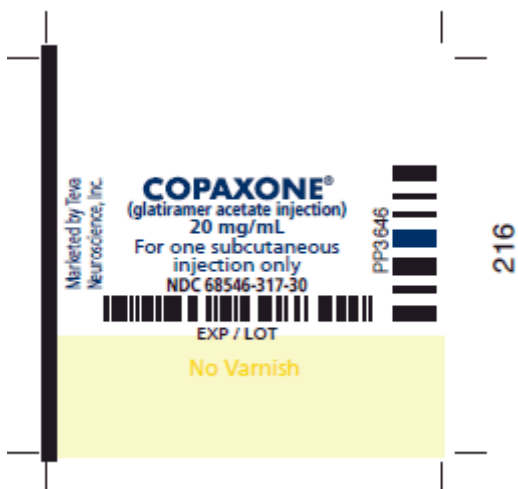
FOR THE RECORD:

1. MODEL LABELING

Labeling based on RLD, Teva's Copaxone (NDA 20-622/S-089 approved 1/28/2014). S-089 provides for a new dosing strength of 40 mg/mL administered three times per week.

S-087 provides for removal of the alcohol preps (swabs) from the Copaxone kit.

20 mg Copaxone labels



LOT: xxxxxx
EXP: mm/yyyy

COPAXONE®
(glatiramer acetate injection)

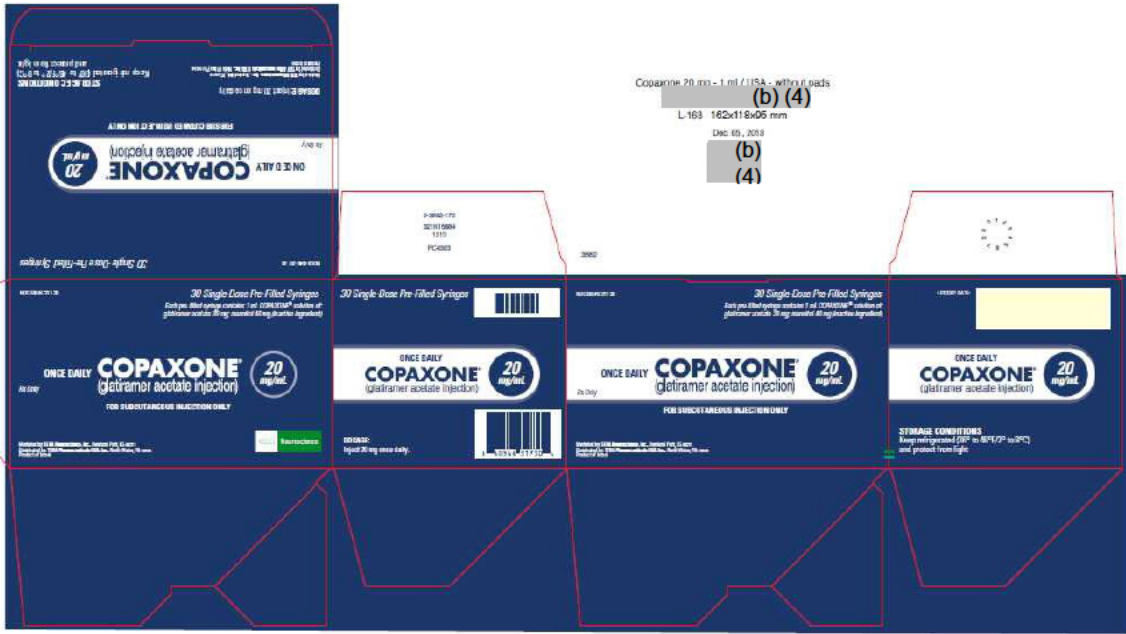
Rx only
Marketed by: TEVA Neuroscience, Inc.,
Overland Park, KS 66211

20 mg/mL

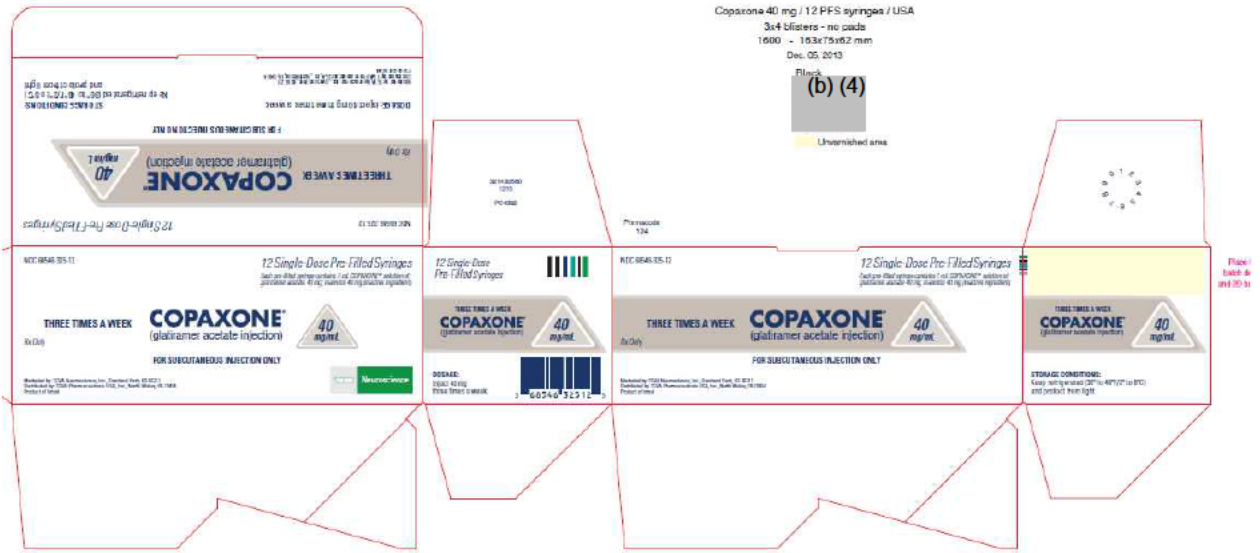
**FOR SUBCUTANEOUS INJECTION ONLY
ONCE DAILY**

NDC 68546-317-30

Each pre-filled syringe contains 1 mL COPAXONE® solution of:
glatiramer acetate 20 mg; mannitol 40 mg (inactive ingredient)
Storage conditions: keep refrigerated (36° to 46°F/2° to 8°C) and protected from light



40 mg Copaxone Labels





Copaxone® (glatiramer acetate injection) 20 mg/1 mL Syringe Blister Text

**COPAXONE®
(glatiramer acetate injection)**

MedWatch – no reference found [checked on March 6, 2014]

2. **USP & PF** [Checked on March 6, 2014] DS and DP are non compendial
3. **PATENT AND EXCLUSIVITY** [Checked on March 6, 2014]

Patent Data – 20622

No	Expiration	Use Code	Use	How filed	Labeling Impact
5981589	May 24, 2014			IV	None
6054430	May 24, 2014			IV	None
6342476	May 24, 2014	U-441	Method of treating MS by administering Copaxone	IV	None
6362161	May 24, 2014	U-441	Method of treating MS by administering Copaxone	IV	None
6620847	May 24, 2014			IV	None

6939539	May 24, 2014			IV	None
7199098	May 24, 2014			IV	None
8367605	May 24, 2014			IV	None

No unexpired exclusivity

Patent amendment dated 11/22/2013: Sandoz and Mylan lost on appeal and court decided that generic companies infringed on the patents. Thus, Sandoz and Mylan could not market until expiration of patents.

4. **INACTIVE INGREDIENTS** [Chem Review #3]

Each 1 mL of glatiramer acetate solution contains 20 mg of glatiramer acetate and the following inactive ingredient 40 mg of mannitol. The pH of the solution is approximately 5.5 to 7.0 [PI]

[Chem Review #3] Glatiramer Acetate Injection 20 mg/mL1 is a clear, colorless to slightly yellow solution of pH ~ 6.9 composed of glatiramer acetate 20 mg and mannitol 40 mg dissolved in water for injection.

Glatiramer acetate is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio.

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide).

Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification.

The major challenge or high risk area is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.

5. **MANUFACTURING FACILITY** [Chem Review #3]

(b) (4)

6. **FINISHED PRODUCT DESCRIPTION AND PRODUCT LINE**

RLD: COPAXONE (glatiramer acetate injection) is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution supplied as:

- 20 mg per mL in a single-dose, prefilled syringe with a white plunger, in individual blister packages supplied in 30-count cartons (NDC 68546-317-30).
- 40 mg per mL in a single-dose, prefilled syringe with a blue plunger, in individual blister packages supplied in 12-count cartons (NDC 68546-325-12).

ANDA: Glatopa (glatiramer acetate injection) is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution in a 1 mL single-dose glass syringe with attached 1/2 inch length and 29 gauge needle supplied as:

- 20 mg per mL in a single-dose, prefilled syringe with a white plunger, in individual blister packages supplied in 30-count cartons with 34 alcohol preps (NDC 0781-3234-34)

7. **STORAGE STATEMENT AND DISPENSING RECOMMENDATIONS**

RLD: Store COPAXONE refrigerated at 2°C to 8°C (36°F to 46°F). If needed, the patient may store COPAXONE at room temperature, 15°C to 30°C (59°F to 86°F), for up to one month, but refrigeration is preferred. Avoid exposure to higher temperatures or intense light. Do not freeze COPAXONE. If a COPAXONE syringe freezes, it should be discarded.

ANDA: Store Glatopa refrigerated at 2°C to 8°C (36°F to 46°F). If needed, the patient may store Glatopa at room temperature, 15°C to 30°C (59°F to 86°F), for up to one month, but refrigeration is preferred. Avoid exposure to higher temperatures or intense light. Do not freeze Glatopa. If a Glatopa syringe freezes, it should be discarded.

8. **CONTAINER/CLOSURE** [Chem Review #2]

3.2.P.7.1 Summary of Packaging System

The primary packaging components consist of a Type 1 glass syringe with a fixed needle and rigid needle shield and a stopper. A plunger rod is applied to the stopper. Details of each component are given in Table 1.

Table 1. Description of Primary Packaging Components

Component	Description	Supplier	DMF
Syringe barrel	Type 1 clear glass barrel with 29 Ga ½ inch fixed needle and (b) (4) rigid needle shield	[REDACTED]	(b) (4)
Stopper	(b) (4) Gray (b) (4)		
Plunger rod	Clear (b) (4)		

9. PATIENT PACKAGE INSERT and INSTRUCTION FOR USE

See comment to firm.

10. RELATED APPLICATIONS- None

11. SPL DATA ELEMENTS

DLDE acceptable in this submission.

12. CITIZENS PETITION/PROPRIETARY NAME/CONSULTS: Yes, Teva submitted CP claiming that generic products are NOT bio-equivalent. The CP is pending with the Agency and the expected response is due on 5/4/2014.

DMEPA found the proprietary name “Glatopa” for Sandoz’s product acceptable (see proprietary name letter dated 1/17/2013).

Sandoz’s 3/4/2014 withdrawal submission pertains to the 1/19/2014 proprietary name logo.

(b) (4)
Sandoz proposed [REDACTED] in the 1/19/2014 submission and in the 12/11/2013 labeling submission.

(b) (4)
In the most recent labeling submission, 2/12/2014, Sandoz proposed [REDACTED].

Thus, I did not review the 12/11/2013 submission b/c Sandoz withdrew the submission per the 3/4/2014 communication.

13. LABELING STATEMENT “ 40 mg/mL are not interchangeable”

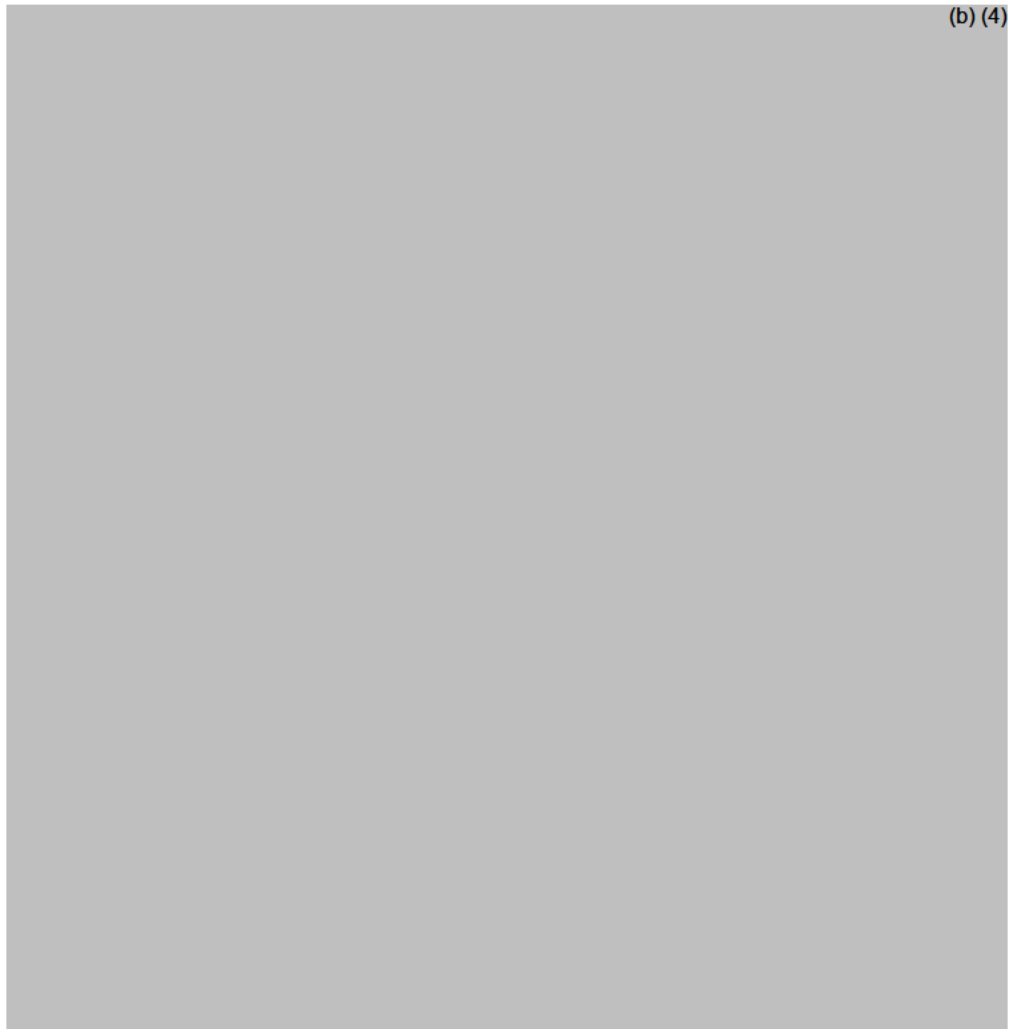
OND recently approved the 40 mg/mL strength for the RLD. The new strength, 40 mg/mL will receive exclusivity (see exclusivity summary dated 1/28/2014). Currently, the exclusivity is NOT posted on the OB. Because of the imminent RLD 40 mg strength exclusivity, the generic labeling will NOT include reference to the 40 mg strength. However, due to safety concerns, “COPAXONE 20 mg per mL and COPAXONE 40 mg per mL are not interchangeable” will be in the Sandoz’s labeling as “Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable”. The phrase will in the Sandoz’s labeling under these

14. **ANDA LABELS**

Syringe Label



Blister Lidding



Carton label



Date of Review: March 6, 2014

Primary Reviewer: Thuyanh Vu

Team Leader: John Grace

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
03/13/2014

JOHN F GRACE
03/14/2014

REVIEW OF PROFESSIONAL LABELING #2
LABELING REVIEW BRANCH
Supercedes LTAP#2

ANDA Number: 090218

Date of Submission: 6/22/2012

Applicant's Name: Sandoz Pharmaceuticals

Established Name: Glatiramer Acetate Injection, 20 mg/1 mL, SD glass syringe with needle

Two Proposed Proprietary Name: (b) (4)

LABELING COMMENTS:

1. GENERAL COMMENT- Your proprietary name labels and labeling are pending review and results may be communicated to you under separate coverage by the Reviewing Division. Should one of your proposed proprietary names become prior to full approval of your application, you may resubmit the requested labeling changes with the proprietary name. We acknowledge submission of established named labels and labeling on 6/25/2012 and will proceed with the labeling review. Should your proprietary name not be approved prior to full approval action, we will be able to use the established name labels and labeling towards final action.
2. CONTAINER DRUG PRODUCT: 20 mg/1 mL - Satisfactory. However, if space permits please add the Rx Only statement. Please provide a diagram and/or actual sample of your syringe.
3. ONE VIAL BLISTER -
 - Please add the needle information. Example. 1 mL single dose ____syringe with attached ____length and ____gauge needle. In addition, add the type of syringe (ex: glass). We are aware the reference product does not include this information. However, since a needle is attached, as part of the package, we feel that information should be included on the labels.
 - The text on the blister is difficult to read because there is underlining text that can be seen from the viewing side of the blister. Please submit labeling that does not impede viewing the labeling on one side or the other.
4. CARTON: Include needle information.
5. PROFESSIONAL PACKAGE INSERT
 - Include needle information in the HOW SUPPLIED section and the type of syringe (glass, .etc)
 - There are areas of blue shade in the insert. Please correct and return the color to black. Example.... See Highlight content section. Please revise through out the insert.

- Please monitor the Drugs@FDA website for updated labeling prior to submitting your amendment. Please site the reference listed drug NDA number, supplement number, and supplement approval date that your insert labeling is modeled after.

6. PATIENT INFORMATION SHEET- Please include needle information.

Please revise your labeling, as instructed above, and submit electronically in draft or final print pdf format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

FOR THE RECORD
LABELING REVIEW BRANCH

REMS required? NO

MedGuides and/or PPIs (505-1(e)) Yes No

Communication plan (505-1(e)) Yes No

Elements to assure safe use (ETASU) (505-1(f)(3)) Yes No

Implementation system if certain ETASU (505-1(f)(4)) Yes No

Timetable for assessment (505-1(d)) for RLD Yes No

ANDA REMS acceptable?

Yes No XNA

1. APPLICANT INFORMATION:

ANDA Number	090218
Date of Submission	
Applicant	Sandoz Pharmaceuticals
Drug Name	Glatiramer Acetate Injection
Strength(s)	20 mg/1 mL Single Dose Syringe with attached needle

Labels and Labeling	
Container 1 mL	FPL Satisfactory in June, 2012
Blister label (1s)	
Carton 30s with 34 alcohol swabs	
Labeling	
Patient	

2. NOTE TO CHEMIST: None.

3. MODEL LABELING- This review was based on the labeling for the RLD.

Reference Listed Drug	
RLD on the 356(h) form	Copaxone
NDA Number	020622
RLD established name	Glatiramer Acetate Injection
Firm	Teva Pharmaceuticals
Currently approved PI	SL-057
AP Date	27 FEB 2009

Note: 2 CR pending supplements. 1 mL syringe.... . Ask applicant to add needle gauge and size and SQ on the blister pack.

4. PATENTS/EXCLUSIVITIES: REFERENCE LISTED DRUG:

Patent Data For NDA

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5981589	May 24, 2014			PIV	Same As
6054430	"			"	"
6342476	"	U-441	METHOD OF TREATING MS BY ADMINISTERING COPAXONE	"	"
6362161	"	U-441	METHOD OF TREATING MS BY ADMINISTERING COPAXONE	"	"
6620847	"	DS		"	"
66939539	"	DS		"	"
7199098	"	DS		"	"

Exclusivity Data For NDA

Code/sup	Expiration	Description	Labeling impact

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM by [REDACTED] (b) (4) for Sandoz in NJ.

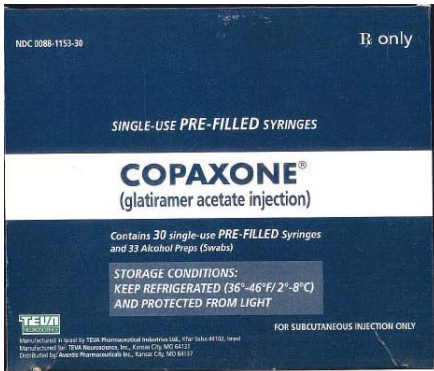
6. CONTAINER/CLOSURE

RLD : COPAXONE® Injection is supplied as a single-use pre-filled syringe containing 1.0 mL of a clear, colorless to slightly yellow, sterile, non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP in cartons of 30 single-use pre-filled syringes, 33 alcohol preps (wipes) and instructions for use. The recommended storage condition for the COPAXONE® Injection is refrigeration (2oC to 8oC / 36oF to 46oF). However, excursions from recommended storage conditions to room temperature conditions (15o to 30oC / 59o to 86o F) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided.

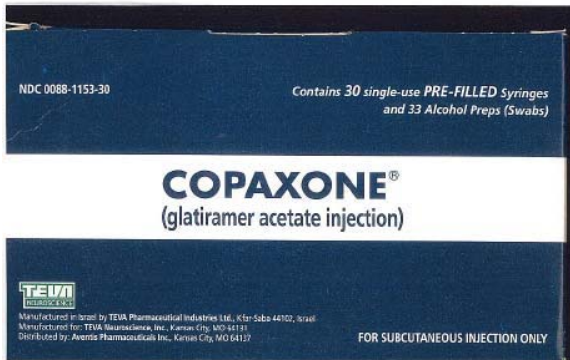




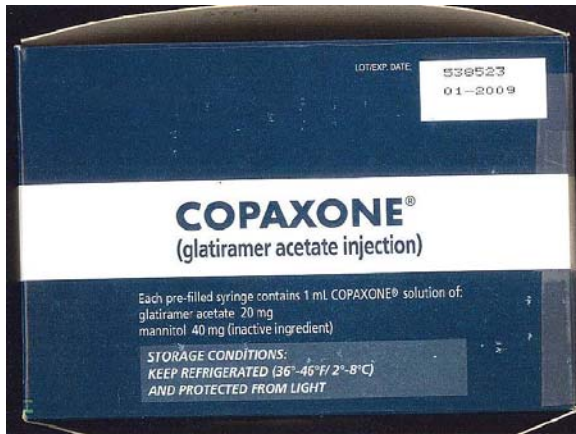
Carton top



Carton side (front)



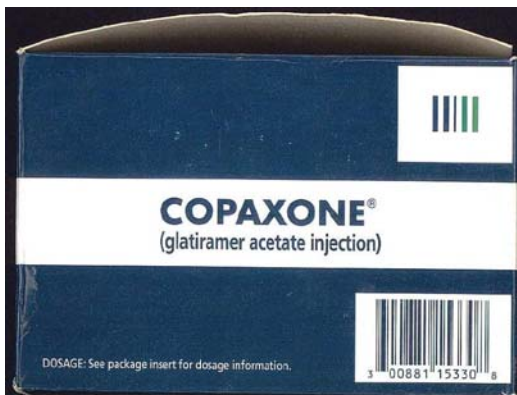
Carton side (right)



Carton side (rear)



Carton Left side



ANDA: 1 mL (b) (4) syringe system. Same description as the RLD.

7. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Glatiramer acetate and Mannitol (inactive) and pH 5.5 to 7.0

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: Not a USP monograph

RLD: Store at 2- 8 (C) excursion permitted 15° - 30°C (59° - 86°F). See USP CRT. Refrigerate.

ANDA: Same as RLD

9. DISPENSING STATEMENTS COMPARISON

USP: Not a USP item.

RLD:

ANDA (*Insert*): Dispense with patient leaflet.

10. BIOAVAILABILITY/BIOEQUIVALENCE:

11. Applicant proposes two different proprietary names for review by DEMPA. The applicant also included the generic established name labels and labeling separately. I will move forward with the generic established labels and labeling review until such time the two proposed names are reviewed by the responsible division. As of 9/26/2012 the proposed name review is pending.

Date of Review: 9/26/12

Date of Submission: 6/22/2012

Primary Reviewer: Angela Payne

Team Leader: John Grace

cc:

ANDA: 090218

DUP/DIVISION FILE

HFD-613/Apayne/JGrace (no cc)

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Review

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/s/

ANGELA M PAYNE

10/03/2012

This na2 review should be included in a CR letter

JOHN F GRACE

10/04/2012

TENTATIVE APPROVAL SUMMARY 2
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	90-218
Date of Submission	04 May 2009
Applicant	Sandoz Pharmaceuticals
Drug Name	Glatiramer Acetate Injection
Strength(s)	20 mg- 1 mL

Labels and Labeling	
Container 1 mL	\\Cdsub1\evsprod\ANDA090218\0004\m1\us\1-14-1-1.pdf
Carton 30s	" "
Labeling	Draft
Patient	Draft

2. NOTE TO CHEMIST: None.

3. MODEL LABELING- This review was based on the labeling for the RLD. See above

Reference Listed Drug	
RLD on the 356(h) form	Copaxone
NDA Number	20-622
RLD established name	Glatiramer Acetate Injection
Firm	Teva Pharmaceuticals
Currently approved PI	SL-26
AP Date	29 AUG 2002
Note: 3 pending supplements (one of the three is a SE-057). Minor change need prior to approval would be to delete the # symbol in the NDC number and add in the 1 mL to the front panel30 single prefilled 1 mL syringe....	

4. PATENTS/EXCLUSIVITIES: REFERENCE LISTED DRUG:

Patent Data For NDA

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5981589	May 24, 2014			PIV	Same As
6054430	"			"	"
6342476	"	U-441	METHOD OF TREATING MS BY ADMINISTERING COPAXONE	"	"
6362161	"	U-441	METHOD OF TREATING MS BY ADMINISTERING COPAXONE	"	"
6620847	"	DS		"	"
66939539	"	DS		"	"
7199098	"	DS		"	"

Exclusivity Data For NDA

Code/sup	Expiration	Description	Labeling impact

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM by [REDACTED] (b) (4) for Sandoz in NJ.

6. CONTAINER/CLOSURE

RLD: COPAXONE® Injection is supplied as a single-use pre-filled syringe containing 1.0 mL of a clear, colorless to slightly yellow, sterile, non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP in cartons of 30 single-use pre-filled syringes, 33 alcohol preps (wipes) and instructions for use. The recommended storage condition for the COPAXONE® Injection is refrigeration (2oC to 8oC / 36oF to 46oF). However, excursions from recommended storage conditions to room temperature conditions (15o to 30oC / 59o to 86o F) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided

ANDA: 1 mL [REDACTED] (b) (4) syringe system. Same description as the RLD.

7. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Glatiramer acetate and Mannitol (inactive) and pH 5.5 to 7.0

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: tight containers

RLD: Store at 2- 8 (C) excursion permitted 15° - 30°C (59° - 86°F). See USP CRT. Refrigerate.

ANDA: Same as RLD

9. DISPENSING STATEMENTS COMPARISON

USP: Not a USP item.

RLD:

ANDA (*Insert*): Dispense with patient leaflet.

10. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 5/15/09
Primary Reviewer: Angela Payne
Team Leader: John Grace

Date of Submission: 04 MAY 2009

cc:

ANDA: 90-218
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Review

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this page is the manifestation of the electronic signature.**

/s/

Angela Payne
5/20/2009 07:56:59 AM
LABELING REVIEWER

John Grace
5/20/2009 10:12:55 AM
LABELING REVIEWER

**REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
Superceds TAP1**

ANDA Number: 90-218 Date of Submission: Jul 07, 2008
Applicant's Name: Sandoz Inc.
Established Name: Glatiramer Acetate Injection 20 mg/mL, Single Use Syringe

Labeling Deficiencies:

1. **CONTAINER** (1 mL): Revise the expression of strength to 20 mg/mL rather than just 20 mg. Please also submit a diagram of your syringe noting calibrations.
2. **BLISTERS (1s)**- Your labeling says protect from light. If the blister does not protect the pre-filled syringe from light we encourage you to add "retain in carton".
3. **CARTON** (30X- 1 mL): Delete the ##s seen in the NDC.
4. **INSERT**: Satisfactory in draft.
5. **PATIENT LEAFLET**: Satisfactory in draft.

Revise your labels and labeling, as instructed above, and submit final printed electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

FOR THE RECORD

LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	90-218
Date of Submission	
Applicant	Sandoz Pharmaceuticals
Drug Name	Glatiramer Acetate Injection
Strength(s)	20 mg- 1 mL

Labels and Labeling	
Container	
1 mL	\\Cdsub1\evsprod\ANDA090218\0000\m1\us\1-14-1-1-carton-contain.pdf
Carton 30s	" "
Labeling	Draft
Patient	Draft

2. NOTE TO CHEMIST: None.

3. MODEL LABELING- This review was based on the labeling for the RLD. See above

Reference Listed Drug	
RLD on the 356(h) form	Copaxone
NDA Number	20-622
RLD established name	Glatiramer Acetate Injection
Firm	Teva Pharmaceuticals
Currently approved PI	SL-26
AP Date	29 AUG 2002
Note: 3 pending supplements (one of the three is a SE-057). Minor change need prior to approval would be to delete the # symbol in the NDC number.	

4. PATENTS/EXCLUSIVITIES: REFERENCE LISTED DRUG:

Patent Data For NDA

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5981589	May 24, 2014			PIV	Same As
6054430	"			"	"
6342476	"	U-441	METHOD OF TREATING MS BY ADMINISTERING COPAXONE	"	"
6362161	"	U-441	METHOD OF TREATING MS BY ADMINISTERING COPAXONE	"	"
6620847	"	DS		"	"
66939539	"	DS		"	"
7199098	"	DS		"	"

Exclusivity Data For NDA

Code/sup	Description	Labeling
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	Expiration		impact

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM by (b) (4) for Sandoz in NJ.

6. CONTAINER/CLOSURE

RLD: COPAXONE® Injection is supplied as a single-use pre-filled syringe containing 1 mL of a clear, colorless to slightly yellow, sterile, non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP in cartons of 30 single-use pre-filled syringes, 33 alcohol preps (wipes) and instructions for use. The recommended storage condition for the COPAXONE® Injection is refrigeration (2oC to 8oC / 36oF to 46oF). However, excursions from recommended storage conditions to room temperature conditions (15o to 30oC / 59o to 86o F) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided,

ANDA: 1 mL (b) (4) syringe system with needle. Same description as the RLD.

7. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Glatiramer acetate and Mannitol (inactive) and pH 5.5 to 7.0

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: tight containers

RLD: Store at 2- 8 (C) excursion permitted 15° - 30°C (59° - 86°F). See USP CRT. Refrigerate.

ANDA: Same as RLD

9. DISPENSING STATEMENTS COMPARISON

USP: Not a USP item.

RLD:

ANDA (*Insert*): Dispense with patient leaflet.

10. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 11/12/08
 Primary Reviewer: Angela Payne
 Team Leader: John Grace

Date of Submission: Jul 7, 2008

cc:

ANDA: 90-218
 DUP/DIVISION FILE
 HFD-613/Apayne/JGrace (no cc)
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 Review

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/s/

Angela Payne
12/4/2008 05:10:45 PM
LABELING REVIEWER

John Grace
12/10/2008 11:25:47 AM
LABELING REVIEWER

TENTATIVE APPROVAL SUMMARY 1
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	90-218
Date of Submission	26 DEC 2007
Applicant	Sandoz Pharmaceuticals
Drug Name	Glatiramer Acetate Injection
Strength(s)	20 mg- 1 mL

Labels and Labeling	
Container	
1 mL	\\Cdsub1\evsprod\ANDA090218\0000\m1\us\1-14-1-1-carton-contain.pdf
Carton 30s	" "
Labeling	Draft
Patient	Draft

2. NOTE TO CHEMIST: None.

3. MODEL LABELING- This review was based on the labeling for the RLD. See above

Reference Listed Drug	
RLD on the 356(h) form	Copaxone
NDA Number	20-622
RLD established name	Glatiramer Acetate Injection
Firm	Teva Pharmaceuticals
Currently approved PI	SL-26
AP Date	29 AUG 2002
Note: 3 pending supplements (one of the three is a SE-057). Minor change need prior to approval would be to delete the # symbol in the NDC number.	

4. PATENTS/EXCLUSIVITIES: REFERENCE LISTED DRUG:

Patent Data For NDA

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5981589	May 24, 2014			PIV	Same As
6054430	"			"	"
6342476	"	U-441	METHOD OF TREATING MS BY ADMINISTERING COPAXONE	"	"
6362161	"	U-441	METHOD OF TREATING MS BY ADMINISTERING COPAXONE	"	"
6620847	"	DS		"	"
66939539	"	DS		"	"
7199098	"	DS		"	"

Exclusivity Data For NDA

Code/sup	Expiration	Description	Labeling impact

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM by (b) (4) for Sandoz in NJ.

6. CONTAINER/CLOSURE

RLD: COPAXONE® Injection is supplied as a single-use pre-filled syringe containing 1.0 mL of a clear, colorless to slightly yellow, sterile, non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP in cartons of 30 single-use pre-filled syringes, 33 alcohol preps (wipes) and instructions for use. The recommended storage condition for the COPAXONE® Injection is refrigeration (2oC to 8oC / 36oF to 46oF). However, excursions from recommended storage conditions to room temperature conditions (15o to 30oC / 59o to 86o F) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided

ANDA: 1 mL (b) (4) syringe system. Same description as the RLD.

7. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. Glatiramer acetate and Mannitol (inactive) and pH 5.5 to 7.0

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: tight containers

RLD: Store at 2- 8 (C) excursion permitted 15° - 30°C (59° - 86°F). See USP CRT. Refrigerate.

ANDA: Same as RLD

9. DISPENSING STATEMENTS COMPARISON

USP: Not a USP item.

RLD:

ANDA (*Insert*): Dispense with patient leaflet.

10. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 9/15/08
Primary Reviewer: Angela Payne
Team Leader: John Grace

Date of Submission: 26 DEC 2007

cc:

ANDA: 90-218
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:\FIRMSNZ\sandoz\LTRS&REV\90218TAP1labdfsreview.doc
Review

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Angela Payne
9/18/2008 02:00:16 PM
LABELING REVIEWER

John Grace
9/22/2008 10:13:47 AM
LABELING REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 090218

CHEMISTRY REVIEWS

**First Generic
Approvable**

Endorsements with Digital Signatures:

Primary Reviewer: Jing Li, PhD	Jing Li -S	<small>Digital Signature of Jing Li DN: cn=Jing Li, o=FDA, ou=CDER, email=jing.li@fda.hhs.gov, c=US</small>
Primary Reviewer: Kshitij (Kris) Patkar, PhD	Kshitij Patkar -S	<small>Digital Signature of Kshitij Patkar DN: cn=Kshitij Patkar, o=FDA, ou=CDER, email=kshitij.patkar@fda.hhs.gov, c=US</small>
Secondary Reviewer: Sau (Larry) Lee, PhD	Sau L. Lee -S	<small>Digital Signature of Sau L. Lee DN: cn=Sau L. Lee, o=FDA, ou=CDER, email=sau.lee@fda.hhs.gov, c=US</small>
Tertiary Reviewer: Andre Raw, PhD	Andre S. Raw -A	<small>Digital Signature of Andre S. Raw DN: cn=Andre S. Raw, o=FDA, ou=CDER, email=andre.raw@fda.hhs.gov, c=US</small>
RBPM: Simon Eng, PharmD	Simon S. Eng -S	<small>Digital Signature of Simon S. Eng DN: cn=Simon S. Eng, o=FDA, ou=CDER, email=simon.s.eng@fda.hhs.gov, c=US</small>

ANDA 090218

**Glatiramer Acetate Injection 20 mg/mL
Sandoz, Inc.**

**Kshitij A. Patkar
Jing Li**

Chemistry: Division I

Table of Contents

Table of Contents	i
Chemistry Review Data Sheet	1
1. ANDA: 090218.....	1
2. REVIEW #: 5.....	1
3. REVIEW DATE: 04/15/2015.....	1
4. REVIEWER: Kshitij Patkar, PhD and Jing Li, PhD	1
5. PREVIOUS DOCUMENTS:.....	1
6. SUBMISSION(S) BEING REVIEWED:	2
7. NAME & ADDRESS OF APPLICANT:	2
8. DRUG PRODUCT NAME/CODE/TYPE:.....	2
9. LEGAL BASIS FOR SUBMISSION:.....	2
10. PHARMACOL. CATEGORY: Immunomodulator.....	2
11. DOSAGE FORM: Injection.....	2
12. STRENGTH/POTENCY: 20 mg/mL	2
13. ROUTE OF ADMINISTRATION: Subcutaneous	2
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):	2
15b. NANOTECHNOLOGY PRODUCT TRACKING:	3
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	3
17. RELATED/SUPPORTING DOCUMENTS:	4
18. STATUS (As of 04/15/2015).....	5
19. ORDER OF REVIEW	5
20. EES INFORMATION - Pending as of 04/15/2015	5
Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8

Basis for Approvability or Not-Approval Recommendation.....	8
SUMMARY OF DATA USED TO SUPPORT DRUG SUBSTANCE SAMENESS OF GLATIRAMER ACETATE	11
Chemistry Assessment.....	12
I. Review of Response to CR Letter dated 08/18//2014 and ECD dated 11/17/2014.....	12
II. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2.....	66
2.3.S.1 General Information.....	66
2.3.S.2 Manufacture	67
2.3.S.3 Characterization	68
2.3.S.4 Control of Drug Substance.....	74
2.3.S.5 Reference Standards or Materials	77
2.3.S.6 Container Closure System.....	77
2.3.S.7 Stability.....	78
2.3.P DRUG PRODUCT [Glatiramer Acetate Injection 20 mg/mL].....	81
2.3.P.1 Description and Composition of the Drug Product.....	81
2.3.P.2 Pharmaceutical Development	82
2.3.P.3 Manufacture	84
2.3.P.4 Control of Excipients	86
2.3.P.5 Control of Drug Product	87
2.3.P.6 Reference Standards or Materials	89
2.3.P.7 Container Closure System.....	89
2.3.P.8 Stability.....	90
A APPENDICES	93
A.1 Facilities and Equipment (biotech only): N/A.....	93
A.2 Adventitious Agents Safety Evaluation: N/A.....	93
A.3 Novel Excipients: N/A.....	93
A.4 Nanotechnology Product Information.....	93
A.5 Precedent Setting Information	93
R REGIONAL INFORMATION	93
R.1 Executed Batch Records (Refer to Sections S.4 and P.5).....	93
R.2 Comparability Protocols: None.....	93
R.3 Methods Validation Package (Refer to Sections S.4 and P.5).....	93
<u>II. Review of Common Technical Document-Quality (Ctd-Q) Module 1.....</u>	<u>94</u>
ADDENDUM: Underlying Chemistry of Polymerization.....	95

Chemistry Review Data Sheet

- 1. ANDA: 090218**
- 2. REVIEW #: 5 (Updated after reviewing response to ECD)**
- 3. REVIEW DATE: 04/15/2015**
- 4. REVIEWER: Kshitij Patkar, PhD and Jing Li, PhD**
- 5. PREVIOUS DOCUMENTS:**

<u>Supporting Document number</u>	<u>Previous Document(s)</u>	<u>Document Date</u>
77	Quality/Quality Information	10/01/2014
76	Correspondence	09/03/2014
75	Meeting/Meeting Request	08/22/2014
74	Meeting/Sponsor Submitted Minutes	07/01/2014
73	Quality/Quality Information Meeting/Meeting Request	06/18/2014
72	Quality/Quality Information	06/10/2014
71	Quality/Quality Information	05/12/2014
70	Response to ECD/Labeling	04/03/2014
69	Labeling/Other	03/27/2014
68	Response to ECD/Labeling	03/26/2014
67	Quality/Quality Information	03/12/2014
66	Withdrawal Request/Supporting Document	03/04/2014
65	Resubmission/ After action-complete; Quality/Microbiology Information; Labeling/Other; Quality/Response To Information Request	02/28/2014
64	Labeling/SPL Final; Labeling/Package Insert Final; Labeling/Container-Carton Final	02/12/2012
63	Proprietary Name/Request For Review	01/09/2014
62	Quality/Response To Information Request	12/12/2013
61	Labeling/Container-Carton Draft, Labeling/Other, Labeling/Package Insert Draft	12/12/2013

Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

<u>Supporting Document number</u>	<u>Submission(s) Reviewed</u>	<u>Document Date</u>
78	Response to ECD/Quality	11/17/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz/Momenta Inc.
Address:	506 Carnegie Center, Suite 400 Princeton, NJ 08540
Representative:	Marcy MacDonald
Telephone:	303-438-4599

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Glatiramer Acetate

9. LEGAL BASIS FOR SUBMISSION:

Innovator product: Copaxone[®]
Innovator Company: Teva Pharmaceuticals
NDA #: 20-622 (Approved on Dec. 20, 1996)

10. PHARMACOL. CATEGORY: Immunomodulator**11. DOSAGE FORM: Injection****12. STRENGTH/POTENCY: 20 mg/mL****13. ROUTE OF ADMINISTRATION: Subcutaneous****14. Rx/OTC DISPENSED:**

Rx OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

NANO product – Form Completed (See Appendix A.4)

Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name(s): L-glutamic acid polymers with L-alanine L-lysine, L-tyrosine (acetate salt)

C.A.S. Registry No.: 147245-92-9

Non-proprietary (USAN/INN) Name: Glatiramer Acetate

Molecular Structure:

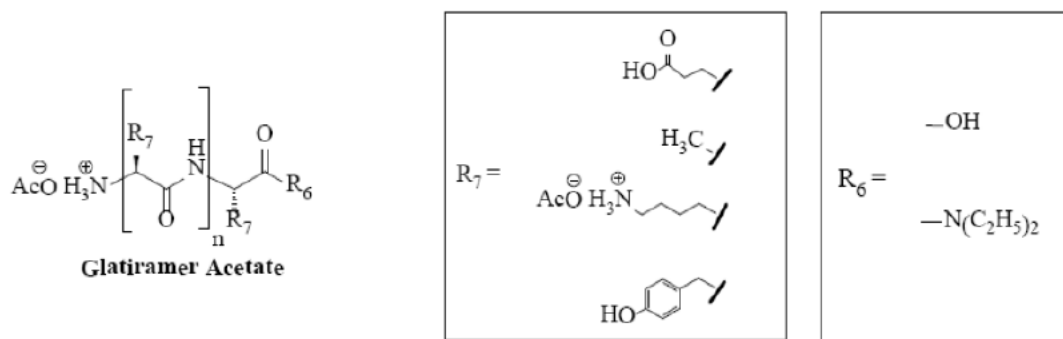


Figure 1. Molecular Structure and Relative Stereochemistry of Glatiramer Acetate

Molecular Formula: (Glu, Ala, Lys, Tyr)_x · xCH₃CO₂H or:
(C₅H₉NO₄.C₃H₇NO₂.C₆H₁₄N₂O₂.C₉H₁₁NO₃)_x · xC₂H₄O₂

Average Molecular weight: 5,000-9,000 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: (As of 04/15/2015)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	1	Adequate	03/31/2014	Reviewed by Palmer-Ochieng, Dupeh G
(b) (4)	III			4			Never reviewed since submission (09/1/2003)
(b) (4)	III			1	Adequate	05/19/2014	Reviewed by Shaw, Arthur B

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS (As of 04/15/2015)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	03/31/2014	Palmer-Ochieng, Dupeh G
EES	See table below		Acceptable
Labeling	Adequate	04/14/2014	Vu, Thuyanh
Bioequivalence	Adequate	10/21/2013	S Pabba
Toxicology/Clinical			
EA	Categorical Exclusions request is made in accordance with 21 CFR 25.31(a). Acceptable	10/10/2014	Kshitij Patkar
Radiopharmaceutical	Not applicable		
Samples Requested	Yes	Per the CR letter dated 11/26/2013	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

20. EES INFORMATION – Acceptable as of 04/15/2015

Drug Substance			
Function	Site Information	FEI/CFN#	Status
(b) (4)		(b) (4)	Acceptable Re-eval. Date: 06/18/2015
Manufacturer			Acceptable Re-eval. Date:06/18/2015
Performs and/or may perform physical, chemical and microbiological testing of drug substance for batch release and stability studies			Acceptable Re-eval Date:11/20/2016
			Acceptable Re-eval Date:04/11/2017
Drug Product			
Function	Site Information	FEI/CFN#	Status



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Drug product manufacturing and packaging Performs and/or may perform physical, chemical and microbiological testing of drug substance and drug product for batch release and stability studies	(b) (4)		(b) (4) Acceptable Re-eval Date: 04/23/2016
Drug product packaging for (b) (4)			Acceptable Re-eval Date:10/26/2015
Glatiramer Acetate Injection manufacturer Testing of drug product for batch release and stability studies	Novartis Vaccines and Diagnostics, Inc. 475 Green Oaks Parkway, Holly Springs, NC 27540	3007867647	Acceptable Re-eval Date:11/21/2015
Performs and/or may perform physical, chemical and microbiological testing of drug substance for batch release and stability studies	(b) (4)		(b) (4) Acceptable Re-eval Date:11/20/2016
Performs and/or may perform chemical and bioassay testing of drug substance and drug product for batch release and stability studies.			Acceptable Re-eval Date:04/11/2017

Overall Re-Evaluation Date 08/16/2015

Chemistry Review for ANDA 090218

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a CMC perspective. The applicant has addressed all the deficiencies satisfactorily.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Sandoz commits to perform post-approval stability testing for Glatiramer Acetate Injection as outlined in the stability protocol

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Glatiramer Acetate Injection 20 mg/mL¹ is a clear, colorless to slightly yellow solution of pH ~ 6.9 composed of glatiramer acetate 20 mg and mannitol 40 mg dissolved in water for injection.

Glatiramer acetate (GA) is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate copolymer are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338, respectively. The purified drug product has an average molecular weight of 5000-9000 Da.

The peptide copolymers in the drug product range from about 40 to 100 amino acids in length. The amino acid sequences and the size of the resultant polypeptides are dependent on factors such as the relative reactivity of the activated amino acid monomers and reaction conditions such as temperature and duration of cleavage process. As a result, the sequences of polypeptides in GA, although not uniform, are not entirely random, and it is expected that certain structural features are highly reproducible under strictly controlled reaction conditions.

¹ Original NDA 20-622

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide). Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification.

The major challenge or high risk area from a CMC perspective is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.

B. Description of How the Drug Product is Intended to be Used

Per the RLD labeling, Glatiramer Acetate is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Glatiramer Acetate is for subcutaneous use only (do not administer intravenously). The recommended dose is 20 mg/day.

	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.1% (20 μ g)	0.15% (30 μ g)
Drug Product	0.2% (40 μ g)	0.5% (100 μ g)

Note that these ICH limits may not be appropriate for the peptide-related substances for this product.

Basis for Approvability or Not-Approval Recommendation

ANDA 90218 is approvable per this review.

Summary of Risk Assessment from a CMC Perspective

Reviews #3-5 which are a continuum, represent the current standards regarding the sameness determination of GA and supersede Reviews 1 and 2.

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide). Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation,

and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification. From a CMC perspective, the major challenge or high risk area is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.

To address this challenge, Sandoz/Momenta have developed an integrated approach for demonstrating the sameness of their drug substance to that in the RLD. This approach is based on understanding and identifying structural fingerprints which reflect the chemical nature of starting materials, and the underlying reaction chemistry and kinetics governing the structural characteristics that are highly reproducible from batch to batch. The structural fingerprints were identified by conducting systematic development studies and utilizing mathematical models. Sandoz/Momenta have developed a set of state-of-art analytics that are capable of characterizing these structural fingerprints. Using this integrated approach, the drug substance sameness for Glatiramer Acetate can be demonstrated between the proposed generic drug and the RLD.

Glatiramer Acetate exhibits some secondary structures but they are thermodynamic in nature (i.e., demonstrating structural reversibility from the thermal and chemical denaturation). Thus, the secondary structures are mainly dependent on the primary structure (in this case defined by structural fingerprints), and are complementary to the structural fingerprints for determination of drug substance sameness for Glatiramer Acetate.

Even though these structural fingerprint data are sufficient to establish the drug substance sameness for Glatiramer Acetate, Sandoz/Momenta also conducted the biocharacterization and gene-expression studies for the confirmatory purposes.

Sandoz/Momenta carried out biocharacterization of Glatiramer Acetate (including experimental autoimmune/allergic encephalomyelitis (EAE) models) and compared the results to the RLD by utilizing the biological and immunological assays. The results do not suggest that there are differences between the Glatiramer Acetate and RLD. However, it should be noted that these biocharacterization tests have their limitations. For example, the relevance of these tests to the clinical effects of Glatiramer Acetate has not been fully elucidated. In addition, they are generally more variable and thus less sensitive to molecular structural differences in the Glatiramer Acetate drug substance.

Sandoz/Momenta also submitted analysis of gene expression data in response to innovator's claim that purported generic glatiramer acetate (obtained outside the U.S.) cannot elicit similar gene expression.² The independent analysis of Teva's gene expression study and Sandoz/Momenta's gene expression data by the Agency (OCP DARS) concluded: (1) the study design of Teva's study was

² Citizen's Petition: FDA-2014-P-0933

flawed, and (2) there were no significant differences between the Sandoz/Momenta proposed Glatiramer Acetate and RLD in gene expression or pathways.

Based on the above sameness characterization data, we conclude that the drug substance, Glatiramer Acetate, manufactured by Sandoz is the same as that in the RLD. Please see the table below for a summary of the data used to establish drug substance sameness of the proposed glatiramer acetate and the RLD.

Based on the pharmaceutical development data, the drug substance manufacturing process is relatively *robust*. In other words, Glatiramer Acetate that is chemically equivalent to the RLD can be produced in relatively wide ranges of process conditions, provided that the starting materials (four NCA amino acids and (b) (4) and chemical reagents (b) (4) used in the proposed process are the same as (or equivalent to) those used to manufacture the RLD, and their quality and quantity are well controlled. The polymerization is carried out until all of NCA amino acids are consumed. The depolymerization is controlled (based on the validated *in situ* (b) (4) measurements in Sandoz/Momenta's process) to meet the target molar mass. The subsequent process steps are also controlled to minimize any side reactions that may impact the structure of Glatiramer Acetate. The control of drug substance with respect to the sameness to RLD is further ensured by incorporating characterization tests for structural fingerprints as part of the drug substance release testing.

The drug product is a simple true solution of the drug substance dissolved in Water for Injection and Mannitol (b) (4). The drug product is a clear, homogeneous liquid where glatiramer acetate is fully dissolved in a solvent (the drug product aqueous formulation) and meets the definitions of a solution as set forth in the FDA Data Standard Manual Dosage Form Monograph and in USP <1151> Pharmaceutical Dosage Forms. It meets the quality standards or expectation for injectables. The drug product is Q1 and Q2 to the RLD so there are no safety concerns regarding the drug product formulation. Aggregation of Glatiramer Acetate Injection drug products was evaluated against the RLD using orthogonal methods. The aggregation study results support that there is no significant aggregation under the recommended storage conditions for both the proposed generic drug product and the RLD. At elevated temperatures, the aggregation for both the proposed generic drug product and RLD is mainly due to the formation of dityrosine crosslinkage.

A APPENDICES

A.1 Facilities and Equipment (biotech only): N/A

A.2 Adventitious Agents Safety Evaluation: N/A

A.3 Novel Excipients: N/A

A.4 Nanotechnology Product Information

A.5 Precedent Setting Information

R REGIONAL INFORMATION

R.1 Executed Batch Records (Refer to Sections S.4 and P.5)

R.2 Comparability Protocols: None

R.3 Methods Validation Package (Refer to Sections S.4 and P.5)

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification Provided: Yes No

Exclusivity Provided: Yes No

Debarment Certification Provided: Yes No

cGMP Statement Provided: Yes No

Reprocessing Statement Provided: Yes No

Letters of Authorization Provided: Yes No

Request for Bio-waiver Provided: Yes No

Citizen Petition and/or Control Request Linked to the Application:

*7 Citizen Petitions filed by Innovator, all have been responded to by the Agency
(except one Citizen Petition that was withdrawn by Innovator)*

8th Citizen Petition was filed by the Innovator on April 1st 2015.

Environmental Impact Considerations/Categorical Exclusions Provided:

Yes No

ADDENDUM 1: UNDERLYING CHEMISTRY OF POLYMERIZATION

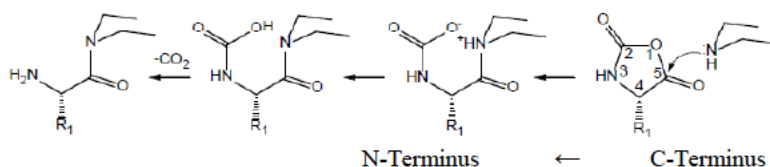
The synthesis of glatiramer acetate involves polymerization of activated forms of amino acids L-alanine (Ala), L-lysine (Lys), L-tyrosine (Tyr) and L-glutamic acid (Glu) in a fixed molar ratio of 0.427, 0.338, 0.141 and 0.095, respectively, in the presence of diethylamine (DEA).⁸ The polymerization step yields an intermediate which is then partially depolymerized and purified to give final glatiramer acetate.

The process of polymerization starts with the initiation of the peptide chains by the reaction of DEA with the *N*-carboxyanhydrides (NCA) forms of the above mentioned amino acids followed by the elongation of the nascent chains by further addition of the NCAs, termed as propagation. The termination of polymerization is brought about by exhaustion of the available NCAs in the reaction mixture.

There are two well-known mechanisms by which the initiation of the polymerization of NCAs can take place.⁹ These include a nucleophilic attack of DEA on each of the NCAs leading to opening of NCA ring and generating another amine. This newly generated amine can act as a nucleophile and further attack another NCA giving rise to propagation of the chain as shown in Figure 1 below. This mechanism is termed as normal amine mechanism (NAM). One of the consequences of chains formed *via* NAM is the presence of diethylated amide at the C-terminal end of each of the peptide chain initiated by the nucleophilic attack on an NCA. NAM proceeds from C-terminus to N-terminus of the growing peptide chain.

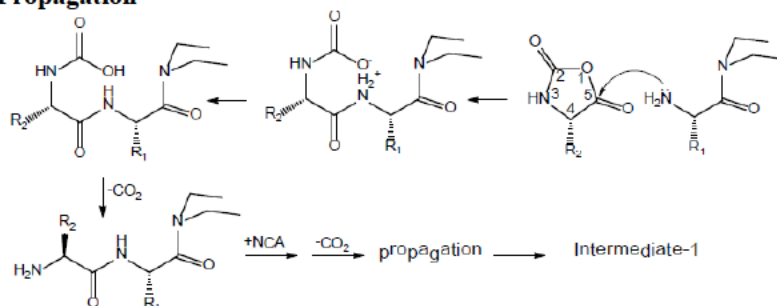
Figure 1: Normal Amine Mechanism (NAM)

Initiation

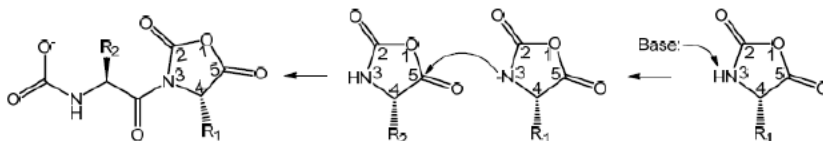
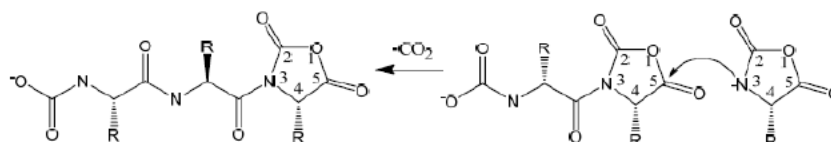


⁸ Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. *European Journal of Immunology* 1971 (1) 242-8.

⁹ (i) Cheng, J.; Deming, T. Synthesis of Polypeptides by Ring-Opening Polymerization of α -Amino Acid N-Carboxyanhydrides. *Top. Curr. Chem.* **2011**, (ii) Goodman, M.; Hutchinson, J. The Mechanisms of N-Unsubstituted N-Carboxyanhydrides. *JACS*, 1966, 3627-30 (iii) Peggion, E.; Terbojevich, M.; Cosani, A. and Colombini, C. mechanism of N-Carboxyanhydride (NCA) Polymerization in Dioxane. Initiation by Carbon-14-Labeled Amines. *JACS*, 1966, 3630-32, (iv) Sekiguchi H, Mechanism of N-carboxy- α -amino acid anhydride (NCA) polymerization, *Pure & Appl. Chem.*, 1981, vol. 53, 1689-1714.

Propagation

The other mechanism involves deprotonation of an NCA to generate NCA anion also called as activated monomer which then acts as a nucleophile to attack another NCA thereby initiating the chain growth. This mechanism is termed as activated monomer mechanism (AMM). However, unlike NAM, the peptide chains formed *via* AMM do not have the characteristic diethylamidated C-termini. In AMM the chains propagate from N- to C-terminus.

Figure 2. Activated Monomer Mechanism (AMM)**Initiation****Propagation**

NAM is a significant mechanism in presence of primary and secondary amines which are strong nucleophiles whereas AMM becomes significant as nucleophilicity of the amine decreases and basicity increases as is seen for tertiary amines¹⁰.

II. Background

Sandoz/Momenta's Glatiramer Acetate (GA) is manufactured by a synthetic process which uses the same four amino acid NCAs as described in the literature. Moreover Sandoz/Momenta's process uses these NCAs (b) (4)

¹⁰ Kircheldorf, H.; Lossov, C.; Schwarz, G. Tertiary Amine Catalyzed Polymerizations of α -Amino Acid N-Carboxyanhydrides: The Role of Cyclization. *J. Polymer Sci.* **2006**, *44*, 4680-95.

Sandoz/Momenta analyzed their manufacturing process for the mechanisms involved in the polymerization. To assess which mechanism is predominantly involved in the initiation of polymerization, Sandoz/Momenta carried out several experiments which are described below.

A. Studies of Initiation Mechanism

(b) (4)



(b) (4)



(b) (4)



(if any) between generic and RLD would be expected to be equivalent given the same fundamental reaction scheme, 2) the remaining criteria to demonstrate sameness rely upon measurements of a comprehensive set of physicochemical properties and structural signatures of glatiramer acetate and a biological assay of the product, and 3) negative controls in which glatiramer acetate is manufactured via different polymerization process conditions and can be distinguished as “not the same” validate the overall sameness criteria.

Annex-I

(b) (4)

ADDENDUM 2

Sandoz's abbreviated new drug application (ANDA 90218) for Glatiramer Acetate (GA) Injection cites the reference listed drug (RLD), Copaxone (GA injection) (NDA 20622), sponsored by Teva Pharmaceuticals (Teva). This addendum provides clarification on instances where information from the NDA 20622 for Copaxone Injection was mentioned in the context of the reviews of ANDA 90218 for GA Injection. The information referenced from the NDA 20622 can be grouped into two conceptual categories.¹¹

The first category of information consists of certain manufacturing process conditions used by Teva in the manufacture of GA as described in NDA 20622. FDA reviewers noted Teva's manufacturing process for GA in the Sandoz ANDA 90218 Chemistry Reviews solely as background information. That information from NDA 20622 was not necessary for the approval of this ANDA.¹² In the review of this ANDA, details of Teva's manufacturing process for GA were not used as a basis for determining active ingredient sameness or other ANDA approval decisions. Active ingredient sameness for GA may be established without comparing, and despite possible differences in, the products' manufacturing processes. The active ingredient sameness determination was based upon equivalence of the following four criteria between the RLD and the proposed ANDA product: (1) fundamental reaction schemes, (2) physicochemical properties, including composition, (3) structural signatures for polymerization and depolymerization, and (4) biological assay.

None of these criteria requires reference to any non-public information about Teva's manufacturing process conditions for Copaxone. For example, an ANDA applicant can satisfy the first criterion (i.e., equivalence in fundamental reaction schemes) using publicly available information on the synthesis process in conjunction with diagnostic analysis of the RLD by orthogonal analytical measurements.¹³ To satisfy the third criterion (equivalence in structural signatures), Sandoz was expected to develop and utilize its own relevant structural signatures for polymerization and depolymerization to determine the process conditions necessary to generate the same active ingredient as Teva's GA. As noted in the Chemistry Reviews for ANDA 90218, many of these structural signatures for polymerization and depolymerization, which are critical to the determination of active ingredient sameness, are minimally impacted by changes in process conditions such as temperature or concentration. As a corollary to this

¹¹ References to these categories of information in the Chemistry Reviews are preceded by the legend, "Not for FOI." This legend is intended to alert CDER's Division of Information Disclosure Policy to the possibility that such information may be subject to redaction prior to production pursuant to a request submitted under the Freedom of Information Act.

¹² We also note that this information was not disclosed to Sandoz or any other ANDA applicant.

¹³ See, e.g., Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide. *European Journal of Immunology*, 1971 (1) 242-248; and US Patent 7,199,098.

observation, there is no expectation that the specific process conditions used by Sandoz to manufacture GA need to be the same as Teva's process conditions.¹⁴

The second category of information consists of Teva's drug substance (active ingredient) and drug product specification standards, such as assay, water content, acetate content, pH, and impurities. These specifications help to ensure that standards for identity, strength, quality, and purity of Teva's GA drug substance and drug product are met. ANDA applicants are expected to develop and submit such standards for the proposed ANDA drug substance and drug product in order to ensure that any generic ANDA that is approved will be held to standards that are adequate to ensure the identity, strength, quality, and purity of the drug.¹⁵ FDA does not disclose to ANDA applicants the product specification standards for the RLD, although FDA may refer to the RLD specifications to confirm that the ANDA's standards are adequate to ensure the identity, strength, quality, and purity of the ANDA product. In this case, the Office of Generic Drugs determined that Sandoz's specifications were adequate to ensure the identity, strength, quality, and purity of the proposed product.

¹⁴ We note that Teva, in a series of citizen petitions, has asserted that "minor differences in . . . the manufacturing process . . . can produce altered polypeptide sequences, which are likely to affect the safety or efficacy of the product." Docket No. FDA-2008-P-0529 (First Citizen Petition), at 32; see also Docket No. FDA-2013-P-1128 (Sixth Citizen Petition), at 8 ("the glatiramer acetate in Copaxone is defined, in large part, by [Teva's] well-controlled manufacturing process."). As part of a thorough review, FDA evaluated some differences between Sandoz's and Teva's process conditions and concluded that the minor differences in process conditions did not preclude a finding of active ingredient sameness. For other products with complex active ingredients, FDA has similarly concluded that differences in manufacturing process do not necessarily preclude a finding of active ingredient sameness. See, e.g., Letter from Woodcock, J. to Zuchero, D., Raubichek, C., and Safir, P. re: Docket No. FDA-2004-P-0494 (Mar. 31, 2011) (relating to ANDAs referencing Ferrlecit).

¹⁵ See, e.g., Guidance for Industry, ANDAs: Impurities in Drug Products (Nov. 2010); Guidance for Industry, ANDAs: Impurities in Drug Substances (June 2009), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm> (e.g., stating that impurities are considered qualified for an ANDA when certain conditions are met, such as the observed level and proposed acceptance criterion for the impurity do not exceed the level justified by the RLD).

ADMINISTRATIVE**Endorsement Block**

Chemist Name/Date: Kshitij A. Patkar

Jing Li

Chemistry Team Leader Name/Date: Sau Lee

Project Manager Name/Date: Simon Eng

TYPE OF LETTER: Approval

CHECKLIST FOR THE CHEMISTRY REVIEW:

090218 Sandoz Glatiramer Acetate Injection

Function	Performed By (Initial and Date)	Check appropriate box
Is this package for new strength PAS?	SE 4-15-15	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
DMF adequate?	SE 4-15-15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No *(see comments)
Any outstanding consults?	SE 4-15-15	<input type="checkbox"/> Yes *(see comments) <input checked="" type="checkbox"/> No
Final recommended dissolution method/specification acknowledged by Firm?	A. Raw	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
Are all facility inspections acceptable?	SE 4-8-15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Is microbiology recommendation adequate for sterile products?	SE 4-8-15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A
Chemistry Post Marketing Agreement (PMA)?	SE 4-8-15	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
If PMA is yes, was OGD informed?	SE 4-8-15	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A
If USP monograph exists, do the specifications conform to the current USP?	A. Raw	<input type="checkbox"/> Yes <input type="checkbox"/> No *(see comments)
Is the final review uploaded into the current IT platform?	SE 4-8-15	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
*Comments -		
No DMF referenced, Drug Substance is in the ANDA		
There is no USP monograph		
Division (Liquid-based Products)	Signature	Date
Andre Raw, Ph.D.	Andre S. Raw -A	Digitally signed by Andre S. Raw -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Andre S. Raw -A, 0.9.2342.19200300.1001.1=1300154978 Date: 2015.04.15 15:39:47 -0400

First Generic
Easily Correctable Deficiency

ANDA 090218

Glatiramer Acetate Injection 20 mg/mL

Sandoz, Inc.

Kshitij A. Patkar
Jing Li

Chemistry: Division I

Table of Contents

Table of Contents	i
Chemistry Review Data Sheet	1
1. ANDA: 090218.....	1
2. REVIEW #: 5.....	1
3. REVIEW DATE: 10/10/2014.....	1
4. REVIEWER: Kshitij Patkar, PhD and Jing Li, PhD	1
5. PREVIOUS DOCUMENTS:.....	1
6. SUBMISSION(S) BEING REVIEWED:	2
7. NAME & ADDRESS OF APPLICANT:	2
8. DRUG PRODUCT NAME/CODE/TYPE:.....	2
9. LEGAL BASIS FOR SUBMISSION:.....	2
10. PHARMACOL. CATEGORY: Immunomodulator.....	2
11. DOSAGE FORM: Injection.....	2
12. STRENGTH/POTENCY: 20 mg/mL	2
13. ROUTE OF ADMINISTRATION: Subcutaneous	2
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):	2
15b. NANOTECHNOLOGY PRODUCT TRACKING:	3
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	3
17. RELATED/SUPPORTING DOCUMENTS:	4
18. STATUS (As of 10/10/2014).....	5
19. ORDER OF REVIEW	5
20. EES INFORMATION - Pending as of	5
Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	8

Basis for Approvability or Not-Approval Recommendation.....	8
Chemistry Assessment.....	11
I. Review of Response to CR Letter dated 08/18//2014	11
II. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2.....	65
2.3.S.1 General Information.....	65
2.3.S.2 Manufacture	66
2.3.S.3 Characterization	67
2.3.S.4 Control of Drug Substance.....	73
2.3.S.5 Reference Standards or Materials	76
2.3.S.6 Container Closure System.....	76
2.3.S.7 Stability	77
2.3.P DRUG PRODUCT [Glatiramer Acetate Injection 20 mg/mL].....	80
2.3.P.1 Description and Composition of the Drug Product.....	80
2.3.P.2 Pharmaceutical Development	81
2.3.P.3 Manufacture	83
2.3.P.4 Control of Excipients	85
2.3.P.5 Control of Drug Product	86
2.3.P.6 Reference Standards or Materials	88
2.3.P.7 Container Closure System.....	899
2.3.P.8 Stability.....	89
A APPENDICES	Error! Bookmark not defined.
A.1 Facilities and Equipment (biotech only): N/A....	Error! Bookmark not defined.
A.2 Adventitious Agents Safety Evaluation: N/A.....	Error! Bookmark not defined.
A.3 Novel Excipients: N/A.....	Error! Bookmark not defined.
A.4 Nanotechnology Product Information... Error! Bookmark not defined.	
A.5 Precedent Setting Information	Error! Bookmark not defined.
R REGIONAL INFORMATION	Error! Bookmark not defined.
R.1 Executed Batch Records (Refer to Sections S.4 and P.5).....	Error! Bookmark not defined.
R.2 Comparability Protocols: None.....	Error! Bookmark not defined.
R.3 Methods Validation Package (Refer to Sections S.4 and P.5).....	Error! Bookmark not defined.
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1.....	Error! Bookmark not defined.
III. List of Deficiencies To Be Communicated.....	94
A. Deficiencies.....	94
B. Information requested.....	93

Chemistry Review Data Sheet

- 1. ANDA: 090218**
- 2. REVIEW #: 5**
- 3. REVIEW DATE: 10/10/2014**
- 4. REVIEWER: Kshitij Patkar, PhD and Jing Li, PhD**
- 5. PREVIOUS DOCUMENTS:**

<u>Supporting Document number</u>	<u>Previous Document(s)</u>	<u>Document Date</u>
76	Correspondence	09/03/2014
75	Meeting/Meeting Request	08/22/2014
74	Meeting/Sponsor Submitted Minutes	07/01/2014
73	Quality/Quality Information Meeting/Meeting Request	06/18/2014
72	Quality/Quality Information	06/10/2014
71	Quality/Quality Information	05/12/2014
70	Response to ECD/Labeling	04/03/2014
69	Labeling/Other	03/27/2014
68	Response to ECD/Labeling	03/26/2014
67	Quality/Quality Information	03/12/2014
66	Withdrawal Request/Supporting Document	03/04/2014
65	Resubmission/ After action-complete; Quality/Microbiology Information; Labeling/Other; Quality/Response To Information Request	02/28/2014
64	Labeling/SPL Final; Labeling/Package Insert Final; Labeling/Container-Carton Final	02/12/2012
63	Proprietary Name/Request For Review	01/09/2014
62	Quality/Response To Information Request	12/12/2013
61	Labeling/Container-Carton Draft, Labeling/Other, Labeling/Package Insert Draft	12/12/2013

6. SUBMISSION(S) BEING REVIEWED:

<u>Supporting Document number</u>	<u>Submission(s) Reviewed</u>	<u>Document Date</u>
77	Quality/ Response to Information request; Resubmission/ After action-complete	10/01/2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz/Momenta Inc.
Address:	506 Carnegie Center, Suite 400 Princeton, NJ 08540
Representative:	Marcy MacDonald
Telephone:	303-438-4599

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
 Non-Proprietary Name (USAN): Glatiramer Acetate

9. LEGAL BASIS FOR SUBMISSION:

Innovator product: Copaxone®
 Innovator Company: Teva Pharmaceuticals
 NDA #: 20-622 (Approved on Dec. 20, 1996)

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED:

Rx OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

NANO product – Form Completed (See Appendix A.4)

Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name(s): L-glutamic acid polymers with L-alanine L-lysine, L-tyrosine (acetate salt)

C.A.S. Registry No.: 147245-92-9

Non-proprietary (USAN/INN) name: Glatiramer Acetate

Molecular Structure:

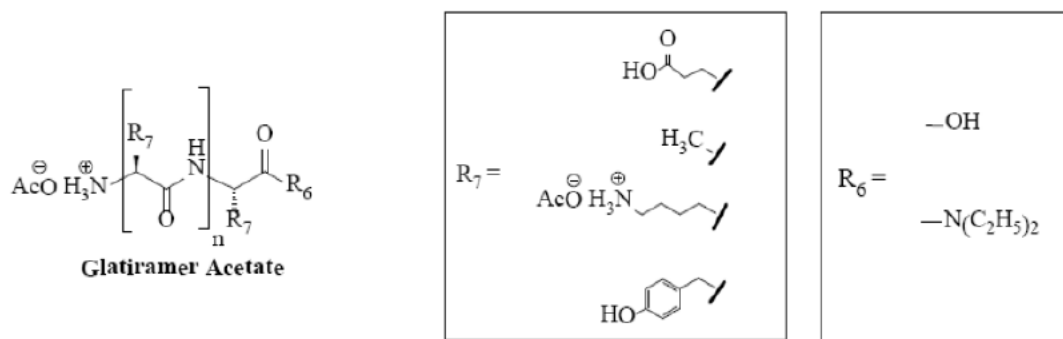


Figure 1. Molecular Structure and Relative Stereochemistry of Glatiramer Acetate

Molecular Formula: (Glu, Ala, Lys, Tyr)_x · xCH₃CO₂H or:
(C₅H₉NO₄ · C₃H₇NO₂ · C₆H₁₄N₂O₂ · C₉H₁₁NO₃)_x · xC₂H₄O₂

Average Molecular weight: 5,000-9,000 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: (As of 11/05/2014)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	03/31//214	Reviewed by Palmer-Ochieng, Dupeh G
(b) (4)	III			4			Never reviewed since submission (09/1/2003)
(b) (4)	III			1	Adequate	05/19/2014	Reviewed by Shaw, Arthur B

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS (As of 10/10/2014)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	03/31/2014	Palmer-Ochieng, Dupeh G
EES	See table below		Acceptable
Labeling	Adequate	04/14/2014	Vu, Thuyanh
Bioequivalence	Adequate	10/21/2013	S Pabba
Toxicology/Clinical			
EA	Categorical Exclusions request is made in accordance with 21 CFR 25.31(a). Acceptable	10/10/2014	Kshitij Patkar
Radiopharmaceutical	Not applicable		
Samples Requested	Yes	Per the CR letter dated 11/26/2013	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

20. EES INFORMATION – Acceptable as of 11/05/2014

Drug Substance			
Function	Site Information	FEI/CFN#	Status
(b) (4)	(b) (4)	(b) (4)	Acceptable Re-eval. Date: 06/18/2015
Manufacturer			Acceptable Re-eval. Date:06/18/2015
Performs and/or may perform physical, chemical and microbiological testing of drug substance for batch release and stability studies			Acceptable Re-eval Date:11/20/2016
			Acceptable Re-eval Date:04/11/2017
Drug Product			



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Function	Site Information	FEI/CFN#	Status
Drug product manufacturing s and packaging Performs and/or may perform physical, chemical and microbiological testing of drug substance and drug product for batch release and stability studies		(b) (4)	Acceptable Re-eval Date: 10/24/2014
Drug product packaging for (b) (4)			Acceptable Re-eval Date:10/26/2015
Glatiramer Acetate Injection manufacturer Testing of drug product for batch release and stability studies	Novartis Vaccines and Diagnostics, Inc. 475 Green Oaks Parkway, Holly Springs, NC 27540	3007867647	Acceptable Re-eval Date:11/21/2015
Performs and/or may perform physical, chemical and microbiological testing of drug substance for batch release and stability studies		(b) (4)	Acceptable Re-eval Date:11/20/2016
Performs and/or may perform chemical and bioassay testing of drug substance and drug product for batch release and stability studies.			Acceptable Re-eval Date:04/11/2017

Chemistry Review for ANDA 090218

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable from a CMC perspective, pending response to easily correctable deficiency.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Sandoz commits to perform post-approval stability testing for Glatiramer Acetate Injection as outlined in the stability protocol

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Glatiramer Acetate Injection 20 mg/mL¹ is a clear, colorless to slightly yellow solution of pH ~ 6.9 composed of glatiramer acetate 20 mg and mannitol 40 mg dissolved in water for injection.

Glatiramer acetate (GA) is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate copolymer are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338, respectively. The purified drug product has an average molecular weight of 5000-9000 Da.

The peptide copolymers in the drug product range from about 40 to 100 amino acids in length. The amino acid sequences and the size of the resultant polypeptides are dependent on factors such as the relative reactivity of the activated amino acid monomers and reaction conditions such as temperature and duration of cleavage process. As a result, the sequences of polypeptides in GA, although not uniform, are not entirely random, and it is expected that certain structural features are highly reproducible under strictly controlled reaction conditions.

¹ Original NDA 20-622

Executive Summary Section

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide). Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification.

The major challenge or high risk area from a CMC perspective is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.

B. Description of How the Drug Product is Intended to be Used

Per the RLD labeling, Glatiramer Acetate is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Glatiramer Acetate is for subcutaneous use only (do not administer intravenously). The recommended dose is 20 mg/day.

	QT (ICH)	IT (ICH)
DS	30 μ g	20 μ g
DP	100 μ g	40 μ g

Note that these ICH limits may not be appropriate for the peptide-related substances for this product.

Basis for Approvability or Not-Approval Recommendation

ANDA 90218 is approvable per this review pending easily correctable deficiency issued.

Summary of Risk Assessment from a CMC Perspective

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide). Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification. From a CMC

Executive Summary Section

perspective, the major challenge or high risk area is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.

To address this challenge, Sandoz/Momenta have developed an integrated approach for demonstrating the sameness of their drug substance to that in the RLD (from the physicochemical perspective). This approach is based on understanding and identification of structural fingerprints which reflect the chemical nature of starting materials, the underlying reaction chemistry and kinetics governing the structural characteristics that are highly reproducible from batch to batch. The structural fingerprints were identified by conducting systematic development studies and utilizing mathematical models. Sandoz/Momenta have developed a set of state-of-art analytics that are capable of characterizing these structural fingerprints. Using this integrated approach, the drug substance sameness for Glatiramer Acetate can be demonstrated between the proposed generic drug and the RLD.

Glatiramer Acetate exhibits some secondary structures but they are thermodynamic in nature (i.e., demonstrating structural reversibility from the thermal and chemical denaturation). It has no tertiary and higher-order structures. Thus, the secondary structures are mainly dependent on the primary structure (in this case defined by structural fingerprints), and are complementary to the structural fingerprints for determination of drug substance sameness for Glatiramer Acetate.

Even though these structural fingerprint data are sufficient to establish the drug substance sameness for Glatiramer Acetate, Sandoz/Momenta also conducted the biocharacterization and gene-expression studies for the confirmatory purposes.

Sandoz/Momenta carried out biocharacterization of Glatiramer Acetate (including experimental autoimmune/allergic encephalomyelitis (EAE) models) and compared the results to the RLD by utilizing the biological and immunological assays. The results do not suggest that there are differences between the Glatiramer Acetate and RLD. However, it should be noted that these biocharacterization tests have their limitations. For example, the relevance of these tests to the clinical effects of Glatiramer Acetate has not been fully elucidated. In addition, they are generally more variable and thus less sensitive to molecular structural differences in the Glatiramer Acetate drug substance.

Sandoz/Momenta also submitted analysis of gene expression data in response to innovator's claim that generic glatiramer acetate cannot elicit similar gene expression.² The independent analysis of Sandoz/Momenta's gene expression data by the Agency (OCP DARS) suggests that there were no reliable differences

² Citizen's Petition: FDA-2014-P-0933

Executive Summary Section

between the proposed Glatiramer Acetate and RLD in gene expression or pathways.

Based on the above sameness characterization data, we conclude that the drug substance, Glatiramer Acetate, manufactured by Sandoz is equivalent to that in the RLD.

Based on the pharmaceutical development data, the drug substance manufacturing process is relatively *robust*. In other words, Glatiramer Acetate that is chemically equivalent to the RLD can be produced in relatively wide ranges of process conditions, provided that the starting materials (four NCA amino acids and (b) (4)) and chemical reagents (b) (4) used in the proposed process are the same as those used to manufacture the RLD, and their quality and quantity are well controlled. The polymerization is carried out until all of NCA amino acids are consumed. The depolymerization is controlled (based on the validated *in situ* (b) (4) measurements in Sandoz/Momenta's process) to meet the target molar mass. The subsequent process steps are also controlled to minimize any side reactions that may impact the structure of Glatiramer Acetate. Based on information from the literature, the proposed process is highly similar to that used to produce the RLD (Note that although this is not the condition for the approval of this ANDA, the similarity between the proposed and innovator processes provide confirmatory evidence of the drug substance sameness). The control of drug substance with respect to the sameness to RLD is further ensured by incorporating characterization tests for structural fingerprints as part of the drug substance release testing.

The drug product is a simple true solution of the drug substance dissolved in Water for Injection and Mannitol (b) (4). It meets the quality standards or expectation for injectables. The drug product is Q1 and Q2 to the RLD so there are no safety concerns regarding the drug product formulation. Aggregation of Glatiramer Acetate Injection drug products was evaluated against the RLD using orthogonal methods. The aggregation study results support that there is no significant aggregation under the recommended storage conditions for both the proposed generic drug product and the RLD. At elevated temperatures, the aggregation for both the proposed generic drug product and RLD is mainly due to the formation of dityrosine crosslinkage.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification Provided: Yes No

Exclusivity Provided: Yes No

Debarment Certification Provided: Yes No

cGMP Statement Provided: Yes No

Reprocessing Statement Provided: Yes No

Letters of Authorization Provided: Yes No

Request for Bio-waiver Provided: Yes No

Citizen Petition and/or Control Request Linked to the Application:

*6 Citizen Petitions filed by Innovator, all have been responded by the Agency
7th Citizen Petition was filed by the Innovator on July 3rd 2014.*

Environmental Impact Considerations/Categorical Exclusions Provided:

Yes No

III. List of Deficiencies To Be Communicated**CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT**

ANDA: 090218

APPLICANT: Sandoz, Inc.

DRUG PRODUCT:

Glatiramer Acetate Injection 20 mg/mL

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows YES NO

A. Deficiencies

1.

(b) (4)

2.

3.

(b) (4)

4.

5.

6.

B. Information Requested

1. Please provide details of analytical method for determining (b) (4)
[redacted] and the validation report for the same.

ADMINISTRATIVE**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Kshitij A. Patkar

Jing Li

Chemistry Team Leader Name/Date: Sau Lee

Project Manager Name/Date: Simon Eng 11-13-14

TYPE OF LETTER: Easily correctable deficiencies



First Generic
Not Approvable – Minor Deficiency

ANDA 090218

Glatiramer Acetate Injection 20 mg/mL

Sandoz, Inc.

Kshitij A. Patkar
Jing Li
Division I, Peptide Team

Table of Contents

Table of Contents	i
Chemistry Review Data Sheet	1
1. ANDA: 090218.....	1
2. REVIEW #: 4.....	1
3. REVIEW DATE: 07/24/2014.....	1
4. REVIEWER: Kshitij Patkar, PhD and Jing Li, PhD	1
5. PREVIOUS DOCUMENTS:.....	1
6. SUBMISSION(S) BEING REVIEWED:	3
7. NAME & ADDRESS OF APPLICANT:	3
8. DRUG PRODUCT NAME/CODE/TYPE:.....	3
9. LEGAL BASIS FOR SUBMISSION:.....	3
10. PHARMACOL. CATEGORY: Immunomodulator.....	3
11. DOSAGE FORM: Injection.....	3
12. STRENGTH/POTENCY: 20 mg/mL	3
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15b. NANOTECHNOLOGY PRODUCT TRACKING:	4
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	4
17. RELATED/SUPPORTING DOCUMENTS:	5
18. STATUS (As of 07/24/2014).....	6
19. ORDER OF REVIEW	6
20. EES INFORMATION - Pending as of 07/24/2014	6
Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	9

Basis for Approvability or Not-Approval Recommendation.....	9
Chemistry Assessment.....	11
I. Review of Response to CR Letter dated 11/27/2013	11
II. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2.....	42
2.3.S.1 General Information.....	39
2.3.S.2 Manufacture	43
2.3.S.3 Characterization	55
2.3.S.4 Control of Drug Substance.....	58
2.3.S.5 Reference Standards or Materials	66
2.3.S.6 Container Closure System.....	69
2.3.S.7 Stability.....	70
2.3.P DRUG PRODUCT [Glatiramer Acetate Injection 20 mg/mL].....	74
2.3.P.1 Description and Composition of the Drug Product.....	74
2.3.P.2 Pharmaceutical Development	75
2.3.P.3 Manufacture	101
2.3.P.4 Control of Excipients	110
2.3.P.5 Control of Drug Product	111
2.3.P.6 Reference Standards or Materials	132
2.3.P.7 Container Closure System.....	134
2.3.P.8 Stability.....	136
A APPENDICES	141
A.1 Facilities and Equipment (biotech only): N/A.....	141
A.2 Adventitious Agents Safety Evaluation: N/A	141
A.3 Novel Excipients: N/A.....	141
A.4 Nanotechnology Product Information.....	141
A.5 Precedent Setting Information	141
R REGIONAL INFORMATION	141
R.1 Executed Batch Records (Refer to Sections S.4 and P.5).....	141
R.2 Comparability Protocols: None.....	141
R.3 Methods Validation Package (Refer to Sections S.4 and P.5).....	141
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1.....	142
III. List of Deficiencies To Be Communicated.....	143
A. Deficiencies.....	143
B. Comments.....	143

Chemistry Review Data Sheet

1. **ANDA: 090218**
2. **REVIEW #: 4**
3. **REVIEW DATE: 07/24/2014**
4. **REVIEWER: Kshitij Patkar, PhD and Jing Li, PhD**
5. **PREVIOUS DOCUMENTS:**

<u>Supporting Document number</u>	<u>Previous Document(s)</u>	<u>Document Date</u>
60	Patent & Exclusivity/Patent Information	11/22/2013
59	Meeting/Meeting Request	4/24/2013
58	Quality/Microbiology Information, Quality/Response To Information Request	1/30/2013
57	Meeting/Meeting Request	1/15/2013
56	Quality/Response To Information Request	12/11/2012
55	Quality/Response To Information Request	12/11/2012
54	Quality/Quality Information	11/30/2012
53	User Fee/Coversheet	11/21/2012
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45	Meeting/Sponsor Submitted Minutes	5/29/2012
44	Meeting/Other	5/8/2012
43	Meeting/Sponsor Submitted Minutes	4/30/2012
42	Meeting/Meeting Package	4/6/2012
41	Correspondence	3/26/2012
40	Correspondence	3/23/2012
39	Meeting/Sponsor Submitted Minutes	3/13/2012
38	Meeting/Meeting Request	2/27/2012
37	Labeling/Container-Carton Draft, Labeling/Package Insert Draft	2/21/2012

Chemistry Review Data Sheet

36	Meeting/Sponsor Submitted Minutes	2/16/2012
35	Meeting/Meeting Package	2/14/2012
34	Meeting/Meeting Package	1/19/2012
33	Correspondence	1/9/2012
32	Meeting/Meeting Request	12/23/2011
31	Meeting/Meeting Package	11/22/2011
30	Meeting/Meeting Request	11/15/2011
29	Proprietary Name/Request for Review	11/8/2011
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26	Meeting/Sponsor Submitted Minutes	9/14/2011
25	Quality/Quality Information	8/11/2011
24	Correspondence	7/22/2011
23	Labeling/Other, Quality/ (b) (4) Information	7/22/2011
22	Correspondence	7/12/2011
21	Correspondence	5/18/2011
20	Meeting/Meeting Request	5/11/2011
19	General Correspondence	4/5/2011
18	Meeting/Meeting Request	3/14/2011
17	Quality/Controls Information	3/4/2011
16	Quality/Response To Information Request	1/18/2011
15	Quality/Response To Information Request	12/20/2010
14	Quality/Response To Information Request	12/13/2010
13	Correspondence	11/24/2010
12	Withdrawal Request- Original/Facility	7/9/2010
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8	Quality/Response To Information Request, Resubmission/After Action- Complete	10/19/2009
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4	Correspondence	3/20/2009
3	Patent & Exclusivity/Patent Information	9/12/2008
2	Labeling/Other	7/9/2008
1	Original Submission	12/27/2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Supporting Document number</u>	<u>Submission(s) Reviewed</u>	<u>Document Date</u>
61, 62	Quality/ Response to Information request; Resubmission/ After action-complete; Labeling/ Package Insert draft; Labeling/Container-carton draft	12/11/2013
65	Quality/Microbiology Information; Resubmission/After Action- Complete; Quality/Response To Information Request; Labeling/Other	02/28/2014
67	Quality/Quality Information	03/12/2014
All previous documents	Drug Substance sections 3.2.S.4, 3.2.S.5, 3.2.S.6, 3.2.S.7 All Drug Product sections	

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz/Momenta Inc.
Address:	506 Carnegie Center, Suite 400 Princeton, NJ 08540
Representative:	Marcy MacDonald
Telephone:	303-438-4599

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: N/A
Non-Proprietary Name (USAN): Glatiramer Acetate

9. LEGAL BASIS FOR SUBMISSION:

Innovator product: Copaxone®
Innovator Company: Teva Pharmaceuticals
NDA #: 20-622 (Approved on Dec. 20, 1996)

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED:

Rx OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

NANO product – Form Completed (See Appendix A.4)

Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name(s): L-glutamic acid polymers with L-alanine L-lysine, L-tyrosine (acetate salt)

C.A.S. Registry No.: 147245-92-9

Non-proprietary (USAN/INN) name: Glatiramer Acetate

Molecular Structure:

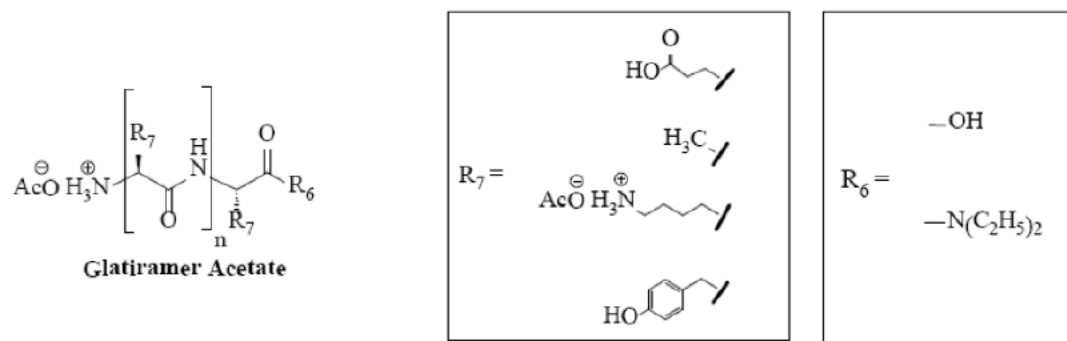


Figure 1. Molecular Structure and Relative Stereochemistry of Glatiramer Acetate

Molecular Formula: $(\text{Glu, Ala, Lys, Tyr})_x \cdot x\text{CH}_3\text{CO}_2\text{H}$ or:
 $(\text{C}_5\text{H}_9\text{NO}_4 \cdot \text{C}_3\text{H}_7\text{NO}_2 \cdot \text{C}_6\text{H}_{14}\text{N}_2\text{O}_2 \cdot \text{C}_9\text{H}_{11}\text{NO}_3)_x \cdot x\text{C}_2\text{H}_4\text{O}_2$

Average Molecular weight: 5,000-9,000 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: (As of 05/05/2014)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	1	Adequate	06/05/214	Reviewed by Wells, Jesse
(b) (4)	III			4			Never reviewed since submission (09/1/2003)
(b) (4)	III			1	Adequate	05/19/2014	Reviewed by Shaw, Arthur B

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS (As of 07/20/2014)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	03/31/2014	Palmer-Ochieng, Dupeh G
EES	See table below		Pending
Labeling	Adequate	04/14/2014	Vu, Thuyanh
Bioequivalence	Adequate	10/21/2013	S Pabba
Toxicology/Clinical			
EA	Categorical Exclusions request is made in accordance with 21 CFR 25.31(a). Acceptable	07/09/2014	Kshitij Patkar
Radiopharmaceutical			
Samples Requested	Yes	Per the CR letter dated 11/26/2013	

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

20. EES INFORMATION - Pending as of 07/20/2014

Drug Substance			
Function	Site Information	FEI/CFN#	Status
(b) (4) Manufacturer		(b) (4)	Request Canceled
(b) (4)			Acceptable
(b) (4) Manufacturer			Acceptable
Performs and/or may perform physical, chemical and microbiological testing of drug substance for batch release and stability studies			Acceptable
			Acceptable

Chemistry Review Data Sheet

	(b) (4)		Acceptable
Drug Product			
Function	Site Information	FEI/CFN#	Status
Drug product manufacturing s and packaging Performs and/or may perform physical, chemical and microbiological testing of drug substance and drug product for batch release and stability studies	(b) (4)		Acceptable
Drug product packaging for (b) (4)			Acceptable
Glatiramer Acetate Injection manufacturer Testing of drug product for batch release and stability studies	Novartis Vaccines and Diagnostics, Inc. 475 Green Oaks Parkway, Holly Springs, NC 27540	3007867647	Acceptable
Secondary packaging site for Novartis	(b) (4)		
Performs and/or may perform physical, chemical and microbiological testing of drug substance for batch release and stability studies			Acceptable
Performs and/or may perform chemical and bioassay testing of drug substance and drug product for batch release and stability studies.			Pending
Drug product manufacturer			Request canceled
Drug product packaging			Request canceled
Performs and/or may perform physical, chemical, bioassay and microbiological testing of drug substance and drug product and excipients for batch release and stability studies.			Request canceled

*The applicant removed (b) (4) as drug product manufacturer in an amendment dated 05/03/2010

Chemistry Review for ANDA 090218

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Sandoz commits to perform post-approval stability testing for Glatiramer Acetate Injection as outlined in the stability protocol

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Glatiramer Acetate Injection 20 mg/mL¹ is a clear, colorless to slightly yellow solution of pH ~ 6.9 composed of glatiramer acetate 20 mg and mannitol 40 mg dissolved in water for injection.

Glatiramer acetate (GA) is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate copolymer are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338 respectively. The purified drug product has an average molecular weight of 5000-9000 Da.

The peptide copolymers in the drug product range from about 40 to 100 amino acids in length. The amino acid sequences and the size of the resultant polypeptides are dependent on factors such as the relative reactivity of the activated amino acid monomers and reaction conditions such as temperature and duration of cleavage process. As a result, the sequences of polypeptides in GA, although not uniform, are not entirely random, and it is expected that certain structural features are highly reproducible under strictly controlled reaction conditions.

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide).

¹ Original NDA 20-622

Executive Summary Section

Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification.

The major challenge or high risk area is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.

B. Description of How the Drug Product is Intended to be Used

Per the RLD labeling, Glatiramer Acetate is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Glatiramer Acetate is for subcutaneous use only (do not administer intravenously). The recommended dose is 20 mg/day.

	QT (ICH)	IT (ICH)
DS	30 µg	20 µg
DP	100 µg	40 µg

Note that these ICH limits may not be appropriate for the peptide-related substances for this product.

Basis for Approvability or Not-Approval Recommendation

ANDA 90218 is not approvable per this review and a **MINOR deficiency** letter is issued.

Summary of Risk Assessment from a CMC Perspective

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide). Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification. *The major challenge or high risk area is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.*

To address this challenge, Sandoz/Momenta have developed an integrated approach for demonstrating the sameness of their drug substance to that in the RLD (from the physicochemical perspective). This approach is based on understanding and identification of structural fingerprints which reflect the chemical nature of starting materials, the underlying reaction chemistry and

Executive Summary Section

kinetics governing the structural characteristics that are highly reproducible from batch to batch. The structural fingerprints were identified by conducting systematic development studies and utilizing mathematical models. Sandoz/Momenta have developed a set of state-of-art analytics that are capable of characterizing these structural fingerprints. Using this integrated approach, the drug substance sameness for Glatiramer Acetate can be demonstrated between the proposed generic and RLD.

Glatiramer Acetate exhibits some secondary structures but they are thermodynamic in nature (i.e., demonstrating structural reversibility from the thermal and chemical denaturation). It has no tertiary and higher-order structures. Thus, these secondary structures are as critical as the structural fingerprints with respect to the determination of drug substance sameness for Glatiramer Acetate.

Based on the pharmaceutical development data, the drug substance manufacturing process is relatively *robust*. In other words, Glatiramer Acetate that is chemically equivalent to the RLD can be produced in relatively wide ranges of process conditions, provided that the starting materials (four NCA amino acids and (b) (4)) and chemical reagents (b) (4) used in the proposed process are the same as those used to manufacture the RLD, and their quality and quantity are well controlled. The polymerization is carried out until all of NCA amino acids are consumed. The depolymerization is controlled (based on *in situ* (b) (4) measurements in Sandoz/Momenta's process) to meet the target molar mass. The subsequent process steps are also controlled to minimize any side reactions that may impact the structure of Glatiramer Acetate. Based on information from the literature, the proposed process is highly similar to that used to produce the RLD. The control of drug substance with respect to the sameness to RLD is further ensured by incorporating characterization tests for structural fingerprints as part of the drug substance release testing.

The drug product is a simple true solution of the drug substance dissolved in Water for Injection and Mannitol (b) (4). The drug product is Q1 and Q2 to the RLD so there are no safety concerns regarding the drug product formulation. Aggregation of Glatiramer Acetate Injection drug products was evaluated against the RLD using orthogonal methods. The aggregation study results support that there is no significant aggregation under the recommended storage conditions for both the proposed generic drug product and the RLD. At elevated temperatures, the aggregation is mainly due to the formation of dityrosine crosslinkages.

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1***Documents***

Patent Certification Provided: Yes No

Exclusivity Provided: Yes No

Debarment Certification Provided: Yes No

cGMP Statement Provided: Yes No

Reprocessing Statement Provided: Yes No

Letters of Authorization Provided: Yes No

Request for Bio-waiver Provided: Yes No

Citizen Petition and/or Control Request Linked to the Application:

*6 Citizen Petitions filed by Innovator, all have been responded by the Agency
7th Citizen Petition was filed by the Innovator on July 3rd 2014.*

Environmental Impact Considerations/Categorical Exclusions Provided:

Yes No

III. List of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090218

APPLICANT: Sandoz, Inc.

DRUG PRODUCT:

Glatiramer Acetate Injection 20 mg/mL

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows YES NO

A. Deficiencies

Review of Response to CR Letters issued on 11/27/2013 and 2/14/2014 to include the comments from the Division of Microbiology

1.

2.

3.

4.

(b) (4)

32.  (b) (4)

33. As part of CDER/OC/OMPQ review of the withhold recommendation from the district, please provide a signed statement that once the stability methods/testing matrix has been finalized in correspondence with OPS, that all methods will be verified at the facilities that will be performing those tests.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. As CDER has committed to address the technical issues regarding stability test methods, OMPQ does not concur with the (b) (4)-DO recommendation to withhold approval of ANDA 90218 due to product-specific deficiencies related to testing of Glatiramer acetate. However if you do not provide a signed statement as detailed above, or your response to OPS regarding stability testing is found inadequate, CDER/OC reserves the right to reverse the decision based upon updated information.
2. Please include a clear and appropriate storage conditions on the label for the drug substance Glatiramer Acetate.
3. Please provide the updated stability data for the validation batches 100M7278, 051M7282, 061M7276 and 071M7276. This data should contain stability studies results for long-term storage conditions at least up to (b) (4) months, since you are proposing (b) (4) months expiration period.
4. We recommend you to specify the acceptance limits for the yield of each manufacturing step and include those in the batch record.

ADMINISTRATIVE**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Kshitij A. Patkar

Jing Li

Chemistry Team Leader Name/Date: Sau Lee

Project Manager Name/Date: Simon Eng 8-15-14

TYPE OF LETTER: Minor deficiencies

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KSHITIJ A PATKAR
08/15/2014

JING LI
08/15/2014

SIMON S ENG
08/15/2014

SAU L LEE
08/15/2014

ANDRE S RAW
08/18/2014

ANDA 090218

Glatiramer Acetate Injection 20 mg/mL

Sandoz/Momenta, Inc.

Kshitij A. Patkar

Jing Li

OGD-Peptide Team

Table of Contents

Table of Contents	i
Chemistry Review Data Sheet	1
1. ANDA: 090218.....	1
2. REVIEW #: 3.....	1
3. REVIEW DATE: 10/09/2013	1
4. REVIEWER: Kshitij Patkar, PhD and Jing Li, PhD	1
5. PREVIOUS DOCUMENTS:.....	1
6. SUBMISSION(S) BEING REVIEWED:	2
7. NAME & ADDRESS OF APPLICANT:	3
8. DRUG PRODUCT NAME/CODE/TYPE:.....	3
9. LEGAL BASIS FOR SUBMISSION: 505(j) RLD NDA # 20622	4
10. PHARMACOL. CATEGORY: Immunomodulator.....	4
11. DOSAGE FORM: Injection.....	4
12. STRENGTH/POTENCY: 20 mg/ mL.....	4
13. ROUTE OF ADMINISTRATION: Subcutaneous	4
14. Rx/OTC DISPENSED: <u> X </u> Rx <u> </u> OTC.....	4
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):	4
15b. NANOTECHNOLOGY PRODUCT TRACKING:	4
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:	5
17. RELATED/SUPPORTING DOCUMENTS:	6
18. STATUS	8
19. ORDER OF REVIEW	8
20. EES INFORMATION	8
I. Recommendations (Non-approvable)	10
A. Recommendation and Conclusion on Approvability.....	10
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B. Description of How the Drug Product Intended to be used	11

Basis for Approvability or Not-Approval Recommendation.....	11
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2.....	13
2.3 Introduction to the Quality Overall Summary	13
2.3.S DRUG SUBSTANCE [Glatiramer Acetate, Sandoz/Momenta].....	14
2.3.S.1 General Information [Glatiramer Acetate, Sandoz/Momenta].....	14
2.3.S.2 Manufacture [Glatiramer Acetate, Sandoz/Momenta]	16
2.3.S.3 Characterization [Glatiramer Acetate, Sandoz/Momenta]	115
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1.....	186
III. List of Deficiencies To Be Communicated.....	187
A. Deficiencies.....	187
B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:.....	191

Chemistry Review Data Sheet

1. ANDA: 090218

2. REVIEW #: 3

3. REVIEW DATE: 10/09/2013

4. REVIEWER: Kshitij Patkar, PhD and Jing Li, PhD

5. PREVIOUS DOCUMENTS:

<u>Supporting Document Number</u>	<u>Previous Document(s)</u>	<u>Document Date</u>
19	General Correspondence	4/5/2011
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7	Correspondence	9/30/2009
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5	Labeling/Other	5/7/2009
4	Correspondence	3/20/2009

Chemistry Review Data Sheet

3	Patent & Exclusivity/Patent Information	9/12/2008
2	Labeling/Other	7/9/2008
1	Original Submission	12/27/2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Supporting Document Number*</u>	<u>Submission(s) Reviewed</u>	<u>Document Date</u>
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34	Meeting/Meeting Package	1/19/2012
35	Meeting/Meeting Package	2/14/2012
36	Meeting/Sponsor Submitted Minutes	2/16/2012
37	Labeling/Container-Carton Draft, Labeling/Package Insert Draft	2/21/2012
38	Meeting/Meeting Request	2/27/2012
39	Meeting/Sponsor Submitted Minutes	3/13/2012
40	Correspondence	3/23/2012
41	Correspondence	3/26/2012
42	Meeting/Meeting Package	4/6/2012
43	Meeting/Sponsor Submitted Minutes	4/30/2012
44	Meeting/Other	5/8/2012

Chemistry Review Data Sheet

45	Meeting/Sponsor Submitted Minutes	5/29/2012
46	Quality/Response To Information Request	6/13/2012
47	Labeling/Container-Carton Draft, Labeling/Other, Labeling/Package Insert Draft	6/25/2012
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57	Meeting/Meeting Request	1/15/2013
58	Quality/Microbiology Information, Quality/Response To Information Request	1/30/2013
59	Meeting/Meeting Request	4/24/2013

* The documents in **BOLD** are the original submission, 1 meeting briefing book, and 3 major Amendments, which the current review focused on.

7. NAME & ADDRESS OF APPLICANT:

Name:	Sandoz/Momenta Inc.
Address:	506 Carnegie Center, Suite 400 Princeton, NJ 08540
Representative:	Srinivas Rao
Telephone:	609-627-8885

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Copaxone®

Non-Proprietary Name (USAN): Glatiramer Acetate



9. LEGAL BASIS FOR SUBMISSION: 505(j) RLD NDA # 20622

10. PHARMACOL. CATEGORY: Immunomodulator

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 20 mg/ mL

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: Rx OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

NANO product – Form Completed (See Appendix A.4)

Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name(s): L-glutamic acid polymers with L-alanine L-lysine, L-tyrosine (acetate salt)

CAS # 147245-92-9

Non-proprietary (USAN/INN) name: Glatiramer Acetate

Molecular Structure:

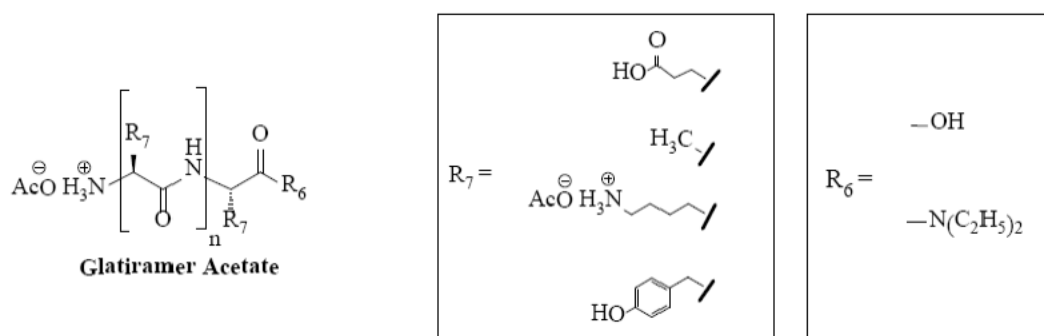


Figure 1. Molecular Structure and Relative Stereochemistry of Glatiramer Acetate

Molecular Formula: Glu, Ala, Lys, Tyr)_x · xCH₃CO₂H or:
 (C₅H₉NO₄ · C₃H₇NO₂ · C₆H₁₄N₂O₂ · C₉H₁₁NO₃)_x · xC₂H₄O₂

Average Molecular weight: 5,000-9,000 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	1	Adequate	8/30/12 by Z Dong (Quality), 11/21/12 by S Donald (Micro)	No new quality information submitted since last review
(b) (4)	III			7			Never reviewed since submission (09/1/2003)
(b) (4)	III				1	Adequate	09/19/2012 E Jao (ONDQA)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Note: DMF (b) (4) was added and DMF (b) (4) was removed per Sandoz/Momenta Amendment dated 1/30/2013

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Adequate	10/15/2010	Theodore Garnett
EES	See table below		Pending
Methods Validation	N/A		
Labeling	Inadequate	10/1/2012	A Payne
Bioequivalence	Adequate	10/21/2013	S Pabba
Toxicology/Clinical	N/A		
EA	N/A		
Radiopharmaceutical	N/A		
Samples requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	Site Information	FEI/CFN#	Status
(b) (4) Manufacturer		(b) (4)	Pending (Assigned inspection)
(b) (4)			Acceptable
Manufacturer			Acceptable
Performs and/or may perform physical, chemical and microbiological testing of drug substance for batch release and stability studies			Acceptable
			Acceptable



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Drug Product			
Function	Site Information	FEI/CFN#	Status
Manufactures drug product and performs secondary packaging of drug product. Performs and/or may perform physical, chemical and microbiological testing of drug product for batch release and stability studies.		(b) (4)	Withheld
Performs and/or may perform physical, chemical and microbiological testing of drug substance for batch release and stability studies		Acceptable	
		Acceptable	

Chemistry Review for ANDA 090218

Executive Summary

I. Recommendations (Non-approvable)

A. Recommendation and Conclusion on Approvability

Not approvable. Major deficiencies related to drug substance sameness. Please refer to below for details.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Glatiramer Acetate Injection 20 mg/mL¹ is a clear, colorless to slightly yellow solution of pH ~ 6.9 composed of glatiramer acetate 20 mg and mannitol 40 mg dissolved in water for injection.

Glatiramer acetate is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate synthesis reaction are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338 respectively. The purified drug product has an average molecular weight of 5000-9000 Da.

The peptide copolymers in the drug product range from about 40 to 100 amino acids in length. The amino acid sequences and the size of the resultant polypeptides are dependent on factors such as the relative reactivity of the activated amino acid monomers and reaction conditions such as temperature and duration of cleavage process. As a result, the sequences of polypeptides in GA, although not uniform, are not entirely random, and it is expected that certain structural features are highly reproducible under strictly controlled reaction conditions.

Glatiramer acetate is a heterogeneous peptide copolymer that is chemically produced by a well-known process that has been published in patents and the literature. The synthesis of glatiramer acetate involves the polymerization of

¹ Original NDA 20-622

Executive Summary Section

the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide). Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization, (5) deprotection, and (6) purification.

The major challenge or high risk area is related to what information we can rely on to demonstrate that the generic and innovator drug products have the same drug substance for this heterogeneous mixture of polypeptides.

B. Description of How the Drug Product Intended to be used

Per the RLD labeling, Glatiramer Acetate is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Glatiramer Acetate is for subcutaneous use only (do not administer intravenously). The recommended dose is 20 mg/day.

	QT (ICH)	IT (ICH)
DS	30 μ g	20 μ g
DP	100 μ g	40 μ g

Note that these ICH limits may not be appropriate for the peptide-related substances for this product.

Basis for Approvability or Not-Approval Recommendation

Not approvable. This review focuses on evaluation of information submitted toward establishing the drug substance sameness from a CMC perspective only. Specifically, it provides an assessment of information regarding the manufacturing process development and characterization of the drug substance. Sandoz/Momenta have presented an integrated approach for demonstrating the sameness of their drug substance to that in the RLD (from the physicochemical perspective). This approach is based on understanding and identification of structural fingerprints, which reflects the chemical nature of starting materials, the underlying reaction chemistry and kinetics governing the structural characteristics that are highly reproducible from batch to batch. The structural fingerprints were identified by conducting systematic development studies and utilizing mathematical models. Sandoz/Momenta have developed a set of state-of-art analytics that are capable of characterizing these structural fingerprints. Using this integrated approach, the drug substance sameness for Glatiramer Acetate can be demonstrated between the

Executive Summary Section

proposed generic and RLD. However, there are still some residual uncertainties in the data supporting the drug substance sameness that warrant further explanation and justification from Sandoz/Momenta, in order to allow us to draw a conclusion regarding drug substance sameness from a physiochemical perspective for this ANDA. We believe that these uncertainties should be resolved with major deficiencies, and once these deficiencies are addressed the remaining CMC sections (including the biocharacterization based on biological and immunological assays that in the reviewers' opinion provide confirmatory evidence of drug substance sameness) will be evaluated.

III. List of Deficiencies To Be Communicated

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90218

APPLICANT: Sandoz/Momenta, Inc.

DRUG PRODUCT: Glatiramer Acetate Injection, 20 mg/mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies

We currently focus on the information you have provided regarding the drug substance manufacturing development and drug substance characterization relevant to the establishment of drug substance sameness for Glatiramer Acetate. We acknowledge your approach of demonstrating the sameness of your proposed drug substance to that in the RLD by understanding and identifying process-related structural signatures through systematic experimental investigation and mathematical modeling. However, there are still some uncertainties about interpretation and quality of some of your data sets. We believe that these uncertainties gave rise to the deficiencies, as summarized below. Upon addressing these deficiencies, we will undertake the review of remaining sections of the drug substance module, including biocharacterization and the drug product in your ANDA.

The manufacture and manufacturing process development of the drug substance have the following deficiencies

1.

(b) (4)

2.

3.

[REDACTED] (b) (4)

19. We acknowledge that you have provided

[REDACTED] (b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response.

1. Please provide samples of your drug substance, drug product, negative controls and the reference product.

2. We also recommend you

[REDACTED] (b) (4)

[REDACTED] of Glatiramer Acetate.

ADMINISTRATIVE**A. Reviewer's Signature****B. Endorsement Block**

Chemist Name/Date: Kshitij A. Patkar Ph.D. and Jing Li, Ph.D. /11-26-2013
Chemistry Team Leader Name/Date: Sau (Larry) Lee
Project Manager Name/Date: Simon Eng

TYPE OF LETTER: MAJOR deficiency

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KSHITIJ A PATKAR
11/26/2013

JING LI
11/26/2013

SAU L LEE
11/26/2013

SIMON S ENG
11/26/2013

ANDRE S RAW
11/26/2013

V:\Chemistry Division I\Team 12\TL Folder\ANDA\Final\90218N00R02C_07-25-11.doc

ANDA 090218

Glatiramer Acetate Injection, 20 mg/mL

Sandoz Inc.

**Eugene L. Schaefer, Ph.D.
Division of Chemistry I**

Review #2C

Table of Contents

The Executive Summary	11
I. Recommendations	11
A. Recommendation and Conclusion on Approvability	11
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	11
II. Summary of Chemistry Assessments.....	11
A. Description of the Drug Product(s) and Drug Substance(s)	11
B. Description of How the Drug Product is Intended to be Used.....	12
C. Basis for Approvability or Not-Approval Recommendation.....	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) 9.....	14
S. DRUG SUBSTANCE.....	14
S.1 General Information 9	14
S.2 Manufacture 10.....	15
P.4 Control of Excipients 64.....	72
P.5 Control of Drug Product.....	73
P.6 Reference Standards	84
P.7 Container Closure System	86
P.8 Drug Product Stability.....	87
A APPENDICES	92
R REGIONAL INFORMATION	92
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	92
A. Labeling & Package Insert	92
B. Environmental Assessment Or Claim Of Categorical Exclusion	93
III. List Of Deficiencies To Be Communicated.....	94

Chemistry Review Data Sheet

1. ANDA 090218
2. REVIEW #: 2C This is a continuation of Review #2A, which was checked into DARRTS on 2/14/11, and Review #2B, which was checked into DARRTS on 6/22/11.
3. REVIEW DATE: 07/20/2011
4. REVIEWER: Eugene L. Schaefer, Ph.D.
5. PREVIOUS DOCUMENTS (reviewed in Chemistry Review #1):

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
2	07/07/2008	Labeling/Other	Original-1	0001
*1	12/26/2007	New/ANDA **	Original-1	0000

6. SUBMISSION(S) BEING REVIEWED*:

(Finished in Chemistry Reviews 2A and 2B)

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
21	05/13/2011	Correspondence ¹²	Original-1	0020
20	05/10/2011	Meeting/Meeting Request ¹¹	General Information-1	0019

Chemistry Review Data Sheet

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
19	04/04/2011	General Correspondence [A Momenta employee raised concerns about the Cell-based Potency Assay.] ¹⁰	General Information-1	0018
*18	03/11/2011	Meeting/Meeting Request [regarding use of (b)(4)] ⁹	General Information-1	0017
*16	01/14/2011	Quality/Response To Information Request [Java codes in ASCII files with .txt extensions] ⁷	Original-1	0015
*15	12/17/2010	Quality/Response To Information Request [Java codes in ASCII files with .txt extensions] ⁶	Original-1	0014
*14	12/09/2010	Quality/Response To Information Request [Java codes and rate constants] ⁵	Original-1	0013
13	11/23/2010	Correspondence [Authorization of (b)(4) to discuss ANDA 090218]	Original-1	0012
*12	07/09/2010	Withdrawal Request- Original/Facility [test site] ⁴	Original-1	0011
10	02/12/2010	General Correspondence [Request for time extension to respond to Microbiology deficiency letter received by Sandoz on 3/11/09]	General Information-1	0009
9	12/14/2009	Meeting/Meeting Request [Regarding possible forfeiture of its 180-day exclusivity if tentative approval is not granted by 6/27/10.]	General Information-1	0008
*8	10/16/2009	Resubmission/After Action- Complete Quality/Response To Information Request ³	Original-1	0007
7	09/30/2009	Correspondence [Second request for time extension to respond to CMC deficiency letter dated 9/15/08]	Original-1	0006

Chemistry Review Data Sheet

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
*6	07/14/2009	General Correspondence [Regarding microbiology deficiencies received by Sandoz on 3/11/09: The drug product manufacturer listed in the ANDA (b) (4) has been discontinued. All future drug product will be manufactured at (b) (4).] ²	General Information-1	0005
*5	05/04/2009	Labeling/Other	Original-1	0004
4	03/18/2009	Correspondence [Request for time extension to respond to CMC deficiency letter dated 9/15/08]	Original-1	0003
3	09/08/2008	Patent & Exclusivity / Patent Information ¹	Original-1	0002

(Finished in Chemistry Review 2C)

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
*17	03/02/2011	Quality/Controls Information [Unsolicited CMC amendment – change to analytical method for Molecular Weight Determination] ⁸	Original-1	0016
*11	04/30/2010	Quality/Microbiology Information²	Original-1	0010
*1	12/26/2007	New/ANDA **	Original-1	0000

The submissions designated in **bold** are the most important submissions covered in Reviews 2A, 2B and 2C.

I finished reviewing the drug substance information in ANDA 090218 in Reviews 2A and 2B. I finished reviewing drug product information in Review 2C.

Chemistry Review Data Sheet

** The first reviewer deferred review of some sections of the original ANDA, and I have reviewed those deferred sections.

¹ The submission of 9/8/08 was submitted before Chemistry Review #1 was finalized. It was not mentioned in Review #1, possibly because the reviewer was not aware of its existence or its content. It contains a discussion of molecular weights and so I thought it should be included in a chemistry review. However, it was written by lawyers and so is not helpful for CMC.

² The Applicant has updated ANDA 090218 with respect to the manufacturer of drug product including process validation information in the submission of 4/30/10. Sandoz has withdrawn the (b) (4) manufacturing site at (b) (4). Supporting Document 11 contains CMC information, including an updated Section 3.2.S.3.1 Elucidation of Structure and other Characteristics.

³ This is the response to the deficiency letter sent after Chemistry Review #1. This submission contains only drug substance information, no drug product information.

⁴ Sandoz has withdrawn the (b) (4) testing site at (b) (4).

⁵ Sandoz has the Java codes available but cannot submit the information because the software extensions are not compatible with FDA systems. Information on temperature dependence of polymerization rate constants is provided in the cover letter.

⁶ Java codes are provided, with instructions, but the codes cannot be accepted for filing. Sandoz's minutes of the teleconference of 11/23/10 are provided. The minutes include limitations of the kinetic models.

⁷ The Java codes are re-submitted, with updated instructions. The submission is successful. The Java codes, and the rate constant information submitted on 12/9/10, are being reviewed by Rebecca Brummitt.

⁸ Sandoz is replacing analytical method (b) (4) which had been used for both release and stability testing of the drug substance and the drug product with TP-300 "Molecular Weight Determination Using SEC-MALS-RI in Glatiramer Acetate and Glatiramer Acetate Injection". The change to TP-300 eliminates the need to (b) (4) (b) (4). This amendment is being submitted to avoid a patent related dispute.

Many sections of the ANDA have been amended as a result of this method change. I have indicated which sections have been amended throughout the review. I have also mentioned this change in Section S.3.1.3.2, even though Sandoz has not amended this section.

Chemistry Review Data Sheet

⁹ Instructions for the [REDACTED] (b) (4) were communicated to Sandoz and the meeting request was denied on 4/28/11.

¹⁰ Momenta engaged an independent law firm to conduct an investigation. The investigation concluded that there were no significant compliance issues associated with the assay.

¹¹ Sandoz has requested a meeting to discuss how they should integrate their response to the deficiency letter we sent with the development work they have been doing. The request has been granted. The tentative date is 8/11/11.

¹² Sandoz authorizes Jim Roach M.D., FACP, FCCP and John Bishop Ph.D., both of Momenta, to address scientific questions that may arise during the review of ANDA 090218 with FDA on behalf of Sandoz.

(Not finished in Chemistry Review 2C)

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
22	07/11/2011	Correspondence	Original-1	0021

The correspondence submitted on 7/11/11 is a briefing book for a meeting scheduled for 8/11/11 between representatives from Sandoz and Momenta and representatives from OGD. Sandoz has stated the objectives of the meeting to be to provide an overview of the changes and improvements to the manufacturing process and characterization of GA, to obtain clarification from the FDA on questions received, and to define a plan for the submission of the response to the deficiency questions in conjunction with the changes to the CTD.

I consider this briefing book to be outside the scope of Review 2C, and I do not want to delay issuing the new deficiencies I have written in Review 2C. I will review the briefing book in a Memorandum to File, and I will check the memo into DARRTS to pass my thoughts to the next reviewer of ANDA 090218, Dr. Huyi Zhang, and my esteemed advisory group.

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Sandoz Inc.
2255 or 2555 West Midway Blvd
Broomfield, CO 80020
Address: The most recent Form 356h lists both street numbers.
Representative: Marcy Macdonald
Director, Regulatory Affairs
Telephone: 303-438-4599
Fax: 303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Copaxone® (Reference Listed Drug)
- b) Non-Proprietary Name (USAN): Glatiramer Acetate Injection

9. LEGAL BASIS FOR SUBMISSION:

Sandoz Inc. (“Sandoz”), by this ANDA, is requesting approval for glatiramer acetate injection; 20 mg/mL (the “Sandoz Product”). Upon information and belief, Sandoz believes that Teva Pharmaceuticals (“Teva”) is the holder of NDA 20-622 for the Approved Listed Drug Product, Copaxone®.

The copy of the Orange Book page provided in the original ANDA says the Copaxone patents expire on 5/24/14, and there is no unexpired exclusivity for this product.

The amendment of 7/7/08 includes a Paragraph IV Certification for seven patents:

"In accordance with 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Sandoz certifies that the claims of said U.S. Patent Nos. 5,981,589, 6,054,430, 6,342,476, 6,362,161, 6,620,847, 6,939,539, and 7,199,098 are invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Sandoz Product."

I did a patent search and found other patents not listed by Sandoz.

The amendment of 9/8/08 contains a Patent Certification Notice in Section 1.3.5.3, FDA Regional Information, Administrative Information, Patent Exclusivity, Exclusivity Request. This is a 28 page document. Pages 15 to 21 discuss molecular weights. I have not found the discussion to be helpful regarding equivalence criteria or acceptance criteria for molecular weight distribution.

Chemistry Review Data Sheet

10. PHARMACOLOGIC CATEGORY: Immunomodulatory agent

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See section S.1.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		LoA dated 11/9/07 submitted 4/30/10
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		LoA dated 11/16/07 submitted 4/30/10

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

Chemistry Review Data Sheet

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

There is no Type II DMF for this ANDA.

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	10/15/10	T.O. Garnett
EES	Pending *		
Methods Validation	Deferred		
Labeling	Acceptable	05/20/09	A.Payne
Bioequivalence	Pending **		
EA	Not Applicable		
Radiopharmaceutical	Not Applicable		

* In our letter sent 2/14/11 we asked Sandoz to formally withdraw the (b) (4) finished dosage packager in (b) (4)

(b) (4) was assigned inspection to IB milestone date 11/4/08. This is still the status as of 7/19/11.

Finished Dosage Manufacturer (b) (4) acceptable 5/16/11.

All other facilities are acceptable.

** Bioequivalence is pending as of 7/19/11.

19. ORDER OF REVIEW

The application submission covered by this review was taken in the date order of receipt.
 ___ Yes ___ X ___ No If no, explain reason(s) below:

The ANDA is being reviewed out of order due to its complexity.

The Chemistry Review for ANDA 090218

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable. Many deficiencies were issued for the drug substance during Reviews 2A and 2B. Review of the drug product has been completed in Review 2C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Glatiramer acetate is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate synthesis reaction are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338 respectively. The purified drug product has an average molecular weight of 5000-9000 Da.

The peptide copolymers in the drug product range from about 40 to 100 amino acids in length and have been described as having “random” sequences. In fact, the sequences are not truly random but rather depend upon the coupling chemistry for the component amino acid monomers. The resultant drug product is, therefore, a mixture of peptide copolymers with defined composition, sequences, and physicochemical properties that are conserved from batch to batch during manufacturing.

Glatiramer acetate is a heterogeneous peptide copolymer that is produced by a well known process that has been published in patents and the literature.^{1,2} The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -

¹ Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. *Eur J Immunol* 1971;1:242-8.

² Teitelbaum D, Gan R, Meshorer A, Hirshfeld T, Arnon R, Sela M, inventors; Therapeutic Copolymer. US patent 3,849,550. 1974.

Executive Summary Section

trifluoroacetic acid amide).³ Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization and (5) deprotection.

B. Description of How the Drug Product is Intended to be Used

Glatiramer acetate is a daily subcutaneous injection indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS).

The Dosage and Administration section of the RLD labeling says:

"The recommended dose of COPAXONE® Injection for the treatment of RRMS is 20 mg/day injected subcutaneously."

Therefore I assume that the Maximum Daily Dose is 20 mg. However, peptides are explicitly not covered by ICH Q3A or Q3B, and glatiramer acetate is a complex mixture of polypeptides.

C. Basis for Approvability or Not-Approval Recommendation

There are CMC deficiencies.

Microbiology is acceptable.

Labeling is acceptable. The manufacturing facility for the finished dosage form was given as (b) (4), so this needs to be updated to (b) (4). I am not writing a new deficiency for this because I hope that Sandoz will be smart enough to make this change when they submit FPL.

EES and bioequivalence are pending.

Methods validation is deferred.

³ The starting materials for glatiramer acetate synthesis are commercially available N-carboxyanhydride derivatives of the four amino acids: alanine, tyrosine, glutamic acid (side-chain protected by an O-benzyl ester), and lysine (side-chain protected by trifluoroacetic acid amide).

Chemistry Assessment Section

I presented sections from the RLD labeling in Review 2A. Now I will present the corresponding sections from Sandoz's draft package insert, which was in the original ANDA and which was found to be acceptable by Angela.

The Description section of the labeling says:

"Glatiramer acetate (b) (4) consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000–9,000 daltons. Glatiramer acetate is identified by specific antibodies."

"Each 1.0 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The pH range of the solution is approximately 5.5 to 7.0. The biological activity of glatiramer acetate is determined by its ability to block the induction of EAE in mice."

The Dosage and Administration section of the labeling says:

(b) (4)

Therefore I assume that the Maximum Daily Dose is 20 mg.

The How Supplied section of the labeling says:

(b) (4)

(b) (4)

B. Environmental Assessment Or Claim Of Categorical Exclusion

Sandoz claimed a categorical exclusion, and certified compliance with all federal, state and local environmental protection requirements, in Section 1.12.14 of the original ANDA.

III. List Of Deficiencies To Be Communicated

See below.

Appears this way on original.

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090218

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Glatiramer Acetate Injection, 20 mg/mL

Review of all information that has been submitted for the drug substance and drug product through Sequence Number 0020, including the updated QOS, has been completed.

Deficiencies regarding the drug substance were communicated to you on February 14 and June 22, 2011. The deficiencies presented below refer to the information submitted regarding the updated QOS and your drug product and are a continuation of the MAJOR deficiencies that we communicated to you on February 14 and June 22, 2011.

A. Deficiencies:

1.

(b) (4)

2.

3.

4.

5.

6.

Following this page, 3 pages withheld in full - (b)(4)

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
 2. An acceptable compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.
 3. Review of your mathematical models is continuing. Additional deficiencies, if any, will be communicated separately.

Sincerely,

{See appended electronic signature page.}

Paul Schwartz, Ph.D.
Acting Director,
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

cc: ANDA 090218

Endorsements:

HFD-625/ELSchaefer, Chemist/

HFD-625/BCai, Team Leader/

HFD-617/EChuh, Project Manager/ [7/27/11 EC](#)

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TYPE OF LETTER: NOT APPROVABLE - MAJOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EUGENE L SCHAEFER
07/27/2011

EUNJUNG E CHUH
07/29/2011

BING CAI
07/29/2011

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ANDA 090218

Glatiramer Acetate Injection, 20 mg/mL

Sandoz Inc.

**Eugene L. Schaefer, Ph.D.
Division of Chemistry I**

Review #2B

Table of Contents

The Executive Summary	11
I. Recommendations	11
A. Recommendation and Conclusion on Approvability	11
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	11
II. Summary of Chemistry Assessments.....	11
A. Description of the Drug Product(s) and Drug Substance(s)	11
B. Description of How the Drug Product is Intended to be Used.....	12
C. Basis for Approvability or Not-Approval Recommendation.....	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) 9.....	22
S. DRUG SUBSTANCE.....	22
S.1 General Information 9	22
S.2 Manufacture 10.....	23
P.4 Control of Excipients 64.....	277
P.5 Control of Drug Product.....	278
P.6 Reference Standards	279
P.7 Container Closure System	279
P.8 Drug Product Stability.....	279
A APPENDICES	280
R REGIONAL INFORMATION	280
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	280
A. Labeling & Package Insert	280
B. Environmental Assessment Or Claim Of Categorical Exclusion	281
III. List Of Deficiencies To Be Communicated.....	282

Chemistry Review Data Sheet

1. ANDA 090218
2. REVIEW #: 2B This is a continuation of Review #2A, which was checked into DARRTS on 2/14/11.
3. REVIEW DATE: 06/21/2011
4. REVIEWER: Eugene L. Schaefer, Ph.D.
5. PREVIOUS DOCUMENTS (reviewed in Chemistry Review #1):

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
2✓	07/07/2008	Labeling/Other	Original-1	0001
*1	12/26/2007	New/ANDA **	Original-1	0000

6. SUBMISSION(S) BEING REVIEWED*:

(Finished in Chemistry Reviews 2A and 2B)

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
21✓	05/13/2011	Correspondence ¹²	Original-1	0020
20✓	05/10/2011	Meeting/Meeting Request ¹¹	General Information-1	0019

Chemistry Review Data Sheet

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
19✓	04/04/2011	General Correspondence [A Momenta employee raised concerns about the Cell-based Potency Assay.] ¹⁰	General Information-1	0018
*18✓	03/11/2011	Meeting/Meeting Request [regarding use of (b)(4)] ⁹	General Information-1	0017
*16✓	01/14/2011	Quality/Response To Information Request [Java codes in ASCII files with .txt extensions] ⁷	Original-1	0015
*15✓	12/17/2010	Quality/Response To Information Request [Java codes in ASCII files with .txt extensions] ⁶	Original-1	0014
*14✓	12/09/2010	Quality/Response To Information Request [Java codes and rate constants] ⁵	Original-1	0013
13✓	11/23/2010	Correspondence [Authorization of (b)(4) to discuss ANDA 090218]	Original-1	0012
*12✓	07/09/2010	Withdrawal Request- Original/Facility [test site] ⁴	Original-1	0011
10✓	02/12/2010	General Correspondence [Request for time extension to respond to Microbiology deficiency letter received by Sandoz on 3/11/09]	General Information-1	0009
9✓	12/14/2009	Meeting/Meeting Request [Regarding possible forfeiture of its 180-day exclusivity if tentative approval is not granted by 6/27/10.]	General Information-1	0008
*8	10/16/2009	Resubmission/After Action- Complete Quality/Response To Information Request ³	Original-1	0007
7✓	09/30/2009	Correspondence [Second request for time extension to respond to CMC deficiency letter dated 9/15/08]	Original-1	0006

Chemistry Review Data Sheet

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
*6✓	07/14/2009	General Correspondence [Regarding microbiology deficiencies received by Sandoz on 3/11/09: The drug product manufacturer listed in the ANDA (b) (4) has been discontinued. All future drug product will be manufactured at (b) (4).] ²	General Information-1	0005
*5✓	05/04/2009	Labeling/Other	Original-1	0004
4✓	03/18/2009	Correspondence [Request for time extension to respond to CMC deficiency letter dated 9/15/08]	Original-1	0003
3✓	09/08/2008	Patent & Exclusivity / Patent Information ¹	Original-1	0002

(Not finished at end of Chemistry Review 2B)

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
*17	03/02/2011	Quality/Controls Information [Unsolicited CMC amendment – change to analytical method for Molecular Weight Determination] ⁸	Original-1	0016
*11	04/30/2010	Quality/Microbiology Information ²	Original-1	0010
*1	12/26/2007	New/ANDA **	Original-1	0000

The submissions designated in **bold** are the most important submissions covered in Reviews 2A and 2B.

Chemistry Review Data Sheet

I am finished with Supporting Document Numbers marked with "✓". I have finished reviewing the drug substance information in ANDA 090218 in Reviews 2A and 2B. I will finish reviewing drug product information in Review 2C.

** The first reviewer deferred review of some sections of the original ANDA, and I am still reviewing those deferred sections which deal with drug product.

¹ The submission of 9/8/08 was submitted before Chemistry Review #1 was finalized. It was not mentioned in Review #1, possibly because the reviewer was not aware of its existence or its content. It contains a discussion of molecular weights and so I thought it should be included in a chemistry review. However, it was written by lawyers and so is not helpful for CMC.

² The Applicant has updated ANDA 090218 with respect to the manufacturer of drug product including process validation information in the submission of 4/30/10. Sandoz has withdrawn the (b) (4) manufacturing site at (b) (4). Supporting Document 11 contains CMC information, including an updated Section 3.2.S.3.1 Elucidation of Structure and other Characteristics.

³ This is the response to the deficiency letter sent after Chemistry Review #1. This submission contains only drug substance information, no drug product information.

⁴ Sandoz has withdrawn the (b) (4) testing site at (b) (4).

⁵ Sandoz has the Java codes available but cannot submit the information because the software extensions are not compatible with FDA systems. Information on temperature dependence of polymerization rate constants is provided in the cover letter.

⁶ Java codes are provided, with instructions, but the codes cannot be accepted for filing. Sandoz's minutes of the teleconference of 11/23/10 are provided. The minutes include limitations of the kinetic models.

⁷ The Java codes are re-submitted, with updated instructions. The submission is successful. The Java codes, and the rate constant information submitted on 12/9/10, are being reviewed by Rebecca Brummitt.

⁸ Sandoz is replacing analytical method (b) (4) which had been used for both release and stability testing of the drug substance and the drug product with TP-300 "Molecular Weight Determination Using SEC-MALS-RI in Glatiramer Acetate and Glatiramer Acetate Injection". The change to TP-300 eliminates the need to (b) (4). This amendment is being submitted to avoid a patent related dispute.

Chemistry Review Data Sheet

Many sections of the ANDA have been amended as a result of this method change. I have indicated which sections have been amended throughout the review. I have also mentioned this change in Section S.3.1.3.2, even though Sandoz has not amended this section.

⁹ Instructions for the [redacted] (b) (4) were communicated to Sandoz and the meeting request was denied on 4/28/11.

¹⁰ Momenta engaged an independent law firm to conduct an investigation. The investigation concluded that there were no significant compliance issues associated with the assay.

¹¹ Sandoz has requested a meeting to discuss how they should integrate their response to the deficiency letter we sent with the development work they have been doing. The request has been granted. The tentative date is 8/11/11.

¹² Sandoz authorizes Jim Roach M.D., FACP, FCCP and John Bishop Ph.D., both of Momenta, to address scientific questions that may arise during the review of ANDA 090218 with FDA on behalf of Sandoz.

7. NAME & ADDRESS OF APPLICANT:

Name: Sandoz Inc.
2255 or 2555 West Midway Blvd
Address: Broomfield, CO 80020
The most recent Form 356h lists both street numbers.
Representative: Marcy Macdonald
Director, Regulatory Affairs
Telephone: 303-438-4599
Fax: 303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Copaxone® (Reference Listed Drug)
- b) Non-Proprietary Name (USAN): Glatiramer Acetate Injection

9. LEGAL BASIS FOR SUBMISSION:

Sandoz Inc. (“Sandoz”), by this ANDA, is requesting approval for glatiramer acetate injection; 20 mg/mL (the “Sandoz Product”). Upon information and belief, Sandoz believes that Teva Pharmaceuticals (“Teva”) is the holder of NDA 20-622 for the Approved Listed Drug Product, Copaxone®.

Chemistry Review Data Sheet

The copy of the Orange Book page provided in the original ANDA says the Copaxone patents expire on 5/24/14, and there is no unexpired exclusivity for this product.

The amendment of 7/7/08 includes a Paragraph IV Certification for seven patents:

"In accordance with 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Sandoz certifies that the claims of said U.S. Patent Nos. 5,981,589, 6,054,430, 6,342,476, 6,362,161, 6,620,847, 6,939,539, and 7,199,098 are invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Sandoz Product."

I did a patent search and found other patents not listed by Sandoz.

The amendment of 9/8/08 contains a Patent Certification Notice in Section 1.3.5.3, FDA Regional Information, Administrative Information, Patent Exclusivity, Exclusivity Request. This is a 28 page document. Pages 15 to 21 discuss molecular weights. I have not found the discussion to be helpful regarding equivalence criteria or acceptance criteria for molecular weight distribution.

10. PHARMACOL. CATEGORY: Immunomodulatory agent

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See section S.1.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	7			Micro Issue
(b) (4)	III			7			(b) (4) not reviewed: secondary container closure system
(b) (4)	III			7			Review of CCS deferred

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Please note that there is no Type II DMF for this ANDA.

B. Other Documents: None

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	10/15/10	T.O. Garnett
EES	Pending *		
Methods Validation	Deferred		
Labeling	Acceptable	05/20/09	A.Payne
Bioequivalence	Pending		
EA	Not Applicable		
Radiopharmaceutical	Not Applicable		

* In our letter sent 2/14/11 we asked Sandoz to formally withdraw the (b) (4) finished dosage packager in (b) (4)

(b) (4) was assigned inspection to IB milestone date 11/4/08. This is still the status as of 6/20/11.

Finished Dosage Manufacturer (b) (4) acceptable 5/16/11.

All other facilities are acceptable.

19. ORDER OF REVIEW

The application submission covered by this review was taken in the date order of receipt.
 ___ Yes ___ X No If no, explain reason(s) below:

The ANDA is being reviewed out of order due to its complexity.

The Chemistry Review for ANDA 090218

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable. Many deficiencies have been issued for the drug substance during Reviews 2A and 2B. Review of the drug product will be completed in Review 2C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Glatiramer acetate is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate synthesis reaction are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338 respectively. The purified drug product has an average molecular weight of 5000-9000 Da.

The peptide copolymers in the drug product range from about 40 to 100 amino acids in length and have been described as having “random” sequences. In fact, the sequences are not truly random but rather depend upon the coupling chemistry for the component amino acid monomers. The resultant drug product is, therefore, a mixture of peptide copolymers with defined composition, sequences, and physicochemical properties that are conserved from batch to batch during manufacturing.

Glatiramer acetate is a heterogeneous peptide copolymer that is produced by a well known process that has been published in patents and the literature.^{1,2} The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -

¹ Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. *Eur J Immunol* 1971;1:242-8.

² Teitelbaum D, Gan R, Meshorer A, Hirshfeld T, Arnon R, Sela M, inventors; Therapeutic Copolymer. US patent 3,849,550. 1974.

Executive Summary Section

trifluoroacetic acid amide).³ Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization and (5) deprotection.

B. Description of How the Drug Product is Intended to be Used

Glatiramer acetate is a daily subcutaneous injection indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS).

The Dosage and Administration section of the RLD labeling says:

"The recommended dose of COPAXONE® Injection for the treatment of RRMS is 20 mg/day injected subcutaneously."

Therefore I assume that the Maximum Daily Dose is 20 mg. However, peptides are explicitly not covered by ICH Q3A or Q3B, and glatiramer acetate is a complex mixture of polypeptides.

C. Basis for Approvability or Not-Approval Recommendation

There are CMC deficiencies.

Microbiology and labeling are acceptable.

EES and bioequivalence are pending.

Methods validation is deferred.

³ The starting materials for glatiramer acetate synthesis are commercially available N-carboxyanhydride derivatives of the four amino acids: alanine, tyrosine, glutamic acid (side-chain protected by an O-benzyl ester), and lysine (side-chain protected by trifluoroacetic acid amide).

Chemistry Assessment Section

I presented sections from the RLD labeling in Review 2A. Now I will present the corresponding sections from Sandoz's draft package insert, which was in the original ANDA and which was found to be acceptable by Angela.

The Description section of the labeling says:

"Glatiramer acetate (b) (4) consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000–9,000 daltons. Glatiramer acetate is identified by specific antibodies."

"Each 1.0 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The pH range of the solution is approximately 5.5 to 7.0. The biological activity of glatiramer acetate is determined by its ability to block the induction of EAE in mice."

The Dosage and Administration section of the labeling says:

(b) (4)

Therefore I assume that the Maximum Daily Dose is 20 mg.

The How Supplied section of the labeling says:

(b) (4)

(b) (4)

B. Environmental Assessment Or Claim Of Categorical Exclusion

Sandoz claimed a categorical exclusion, and certified compliance with all federal, state and local environmental protection requirements, in Section 1.12.14 of the original ANDA.

III. List Of Deficiencies To Be Communicated

See below.

Appears this way on original.

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090218

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Glatiramer Acetate Injection, 20 mg/mL

Review of all information that has been submitted for the drug substance until now has been completed. Review of drug product information is continuing. Further deficiencies, if any, will be communicated separately.

The deficiencies presented below represent a continuation of the MAJOR deficiencies that we communicated to you on February 14, 2011.

A. Deficiencies:

1.

2.

3.

4.

(b) (4)

Following this page, 15 pages withheld in full - (b)(4)

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

55.  (b) (4)

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
 2. An acceptable compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.
 3. Review of your mathematical models is continuing. Additional deficiencies, if any, will be communicated separately.

Sincerely,

{See appended electronic signature page.}

Paul Schwartz, Ph.D.
Acting Director,
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

cc: ANDA 090218

Endorsements:

HFD-625/ELSchaefer, Chemist/

HFD-625/BCai, Team Leader/

HFD-617/EChuh, Project Manager/

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TYPE OF LETTER: NOT APPROVABLE - MAJOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EUGENE L SCHAEFER
06/22/2011

EUNJUNG E CHUH
06/22/2011

BING CAI
06/22/2011

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ANDA 090218

Glatiramer Acetate Injection, 20 mg/mL

Sandoz Inc.

**Eugene L. Schaefer, Ph.D.
Division of Chemistry I**

Review #2A

Table of Contents

The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
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Chemistry Assessment	11
I. Review Of Common Technical Document-Quality (Ctd-Q) 9.....	23
S. DRUG SUBSTANCE.....	23
S.1 General Information 9	23
S.2 Manufacture 10.....	23
P.4 Control of Excipients 64.....	235
P.5 Control of Drug Product.....	235
P.6 Reference Standards	236
P.7 Container Closure System	236
P.8 Drug Product Stability.....	236
A APPENDICES	237
R REGIONAL INFORMATION	237
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	237
A. Labeling & Package Insert	237
B. Environmental Assessment Or Claim Of Categorical Exclusion	238
III. List Of Deficiencies To Be Communicated.....	238

Chemistry Review Data Sheet

1. ANDA 090218
2. REVIEW #: 2
3. REVIEW DATE:
4. REVIEWER: Eugene L. Schaefer, Ph.D.
5. PREVIOUS DOCUMENTS:

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
2	07/07/2008	Labeling/Other	Original-1	0001
1	12/26/2007	New/ANDA	Original-1	0000

6. SUBMISSION(S) BEING REVIEWED*:

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
16	01/14/2011	Quality/Response To Information Request [Java codes in ASCII files with .txt extensions]	Original-1	0015
15	12/17/2010	Quality/Response To Information Request [Java codes in ASCII files with .txt extensions]	Original-1	0014

Chemistry Review Data Sheet

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
14	12/09/2010	Quality/Response To Information Request [Java codes]	Original-1	0013
13	11/23/2010	Correspondence [Authorization of (b) (4) to discuss ANDA 090218]	Original-1	0012
*12	07/09/2010	Withdrawal Request- Original/Facility [test site]	Original-1	0011
*11	04/30/2010	Quality/Microbiology Information ***	Original-1	0010
10	02/12/2010	General Correspondence [Request for time extension to respond to Microbiology deficiency letter received by Sandoz on 3/11/09]	General Information-1	0009
9	12/14/2009	Meeting/Meeting Request [Regarding possible forfeiture of its 180-day exclusivity if tentative approval is not granted by 6/27/10.]	General Information-1	0008
*8	10/16/2009	Resubmission/After Action- Complete Quality/Response To Information Request	Original-1	0007
7	09/30/2009	Correspondence [Second request for time extension to respond to CMC deficiency letter dated 9/15/08]	Original-1	0006
*6	07/14/2009	General Correspondence [Regarding microbiology deficiencies received by Sandoz on 3/11/09: The drug product manufacturer listed in the ANDA (b) (4) has been discontinued. All future drug product will be manufactured at (b) (4) (b) (4).] ***	General Information-1	0005
5	05/04/2009	Labeling/Other	Original-1	0004

Chemistry Review Data Sheet

Supporting Document Number	Submit Date	Supporting Document Category / Subcategory	Submission Type-Number (Classification)	Location (Volume or e-CTD Sequence Number)
4	03/18/2009	Correspondence [Request for time extension to respond to CMC deficiency letter dated 9/15/08]	Original-1	0003
*3	09/08/2008	Patent & Exclusivity/Patent Information **	Original-1	0002

The submissions designated in **bold** are the most important submissions covered in this review.

** The submission of 9/8/08 was submitted before Chemistry Review #1 was finalized. It was not mentioned in Review #1, possibly because the reviewer was not aware of its existence or its content. It contains a discussion of molecular weights and so should be included in a chemistry review.

*** The Applicant has updated ANDA 090218 with respect to the manufacturer of drug product including process validation information in the submission of 4/30/10. Supporting Document 11 contains CMC information, including an updated Section 3.2.S.3.1 Elucidation of Structure and other Characteristics.

7. NAME & ADDRESS OF APPLICANT:

Name: Sandoz Inc.
 2255 or 2555 West Midway Blvd
 Broomfield, CO 80020
 Address: The most recent Form 356h lists both street numbers.
 Representative: Marcy Macdonald
 Director, Regulatory Affairs
 Telephone: 303-438-4599
 Fax: 303-438-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Copaxone® (Reference Listed Drug)
- b) Non-Proprietary Name (USAN): Glatiramer Acetate Injection

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

Sandoz Inc. (“Sandoz”), by this ANDA, is requesting approval for glatiramer acetate injection; 20 mg/mL (the “Sandoz Product”). Upon information and belief, Sandoz believes that Teva Pharmaceuticals (“Teva”) is the holder of NDA 20-622 for the Approved Listed Drug Product, Copaxone®.

The copy of the Orange Book page provided in the original ANDA says the Copaxone patents expire on 5/24/14, and there is no unexpired exclusivity for this product.

The amendment of 7/7/08 includes a Paragraph IV Certification for seven patents:

"In accordance with 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Sandoz certifies that the claims of said U.S. Patent Nos. 5,981,589, 6,054,430, 6,342,476, 6,362,161, 6,620,847, 6,939,539, and 7,199,098 are invalid, unenforceable, and/or will not be infringed by the manufacture, use or sale of the Sandoz Product."

I did a patent search and found other patents not listed by Sandoz.

The amendment of 9/8/08 contains a Patent Certification Notice in Section 1.3.5.3, FDA Regional Information, Administrative Information, Patent Exclusivity, Exclusivity Request. This is a 28 page document. Pages 15 to 21 discuss molecular weights. I have not read these pages in detail, but I might want to come back to them some time.

10. PHARMACOL. CATEGORY: Immunomodulatory agent

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See section S.1.

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	7			Micro Issue
(b) (4)	III			7			(b) (4) not reviewed: secondary container closure system
(b) (4)	III			7			Review of CCS deferred

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Please note that there is no Type II DMF for this ANDA.

B. Other Documents: None

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	10/15/10	T.O. Garnett
EES	Pending *		
Methods Validation	Deferred		
Labeling	Acceptable	05/20/09	A.Payne
Bioequivalence	Pending		
EA	Not Applicable		
Radiopharmaceutical	Not Applicable		

* I am asking Sandoz to formally withdraw the (b) (4) finished dosage packager in (b) (4)

(b) (4) was assigned inspection to IB milestone date 11/4/08.

All other facilities are acceptable.

19. ORDER OF REVIEW

The application submission covered by this review was taken in the date order of receipt.
 ___ Yes ___ X ___ No If no, explain reason(s) below:

The ANDA is being reviewed out of order due to its complexity.

The Chemistry Review for ANDA 090218

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable. The applicant's evidence to demonstrate sameness of the generic glatiramer acetate as compared to Copaxone® needs improvement. For this reason, review of other sections of the ANDA are being deferred.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Glatiramer acetate is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate synthesis reaction are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338 respectively. The purified drug product has an average molecular weight of 5000-9000 Da.

The peptide copolymers in the drug product range from about 40 to 100 amino acids in length and have been described as having “random” sequences. In fact, the sequences are not truly random but rather depend upon the coupling chemistry for the component amino acid monomers. The resultant drug product is, therefore, a mixture of peptide copolymers with defined composition, sequences, and physicochemical properties that are conserved from batch to batch during manufacturing.

Glatiramer acetate is a heterogeneous peptide copolymer that is produced by a well known process that has been published in patents and the literature.^{1,2} The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of

¹ Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. *Eur J Immunol* 1971;1:242-8.

² Teitelbaum D, Gan R, Meshorer A, Hirshfeld T, Arnon R, Sela M, inventors; Therapeutic Copolymer. US patent 3,849,550. 1974.

Executive Summary Section

the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide).³ Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization and (5) deprotection.

B. Description of How the Drug Product is Intended to be Used

Glatiramer acetate is a daily subcutaneous injection indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS).

The Dosage and Administration section of the RLD labeling says:

"The recommended dose of COPAXONE® Injection for the treatment of RR MS is 20 mg/day injected subcutaneously."

Therefore I assume that the Maximum Daily Dose is 20 mg. However, peptides are explicitly not covered by ICH Q3A or Q3B, and glatiramer acetate is a complex mixture of polypeptides.

C. Basis for Approvability or Not-Approval Recommendation

There are CMC deficiencies.

Microbiology and labeling are acceptable.

EES and bioequivalence are pending.

Methods validation is deferred.

³ The starting materials for glatiramer acetate synthesis are commercially available N-carboxyanhydride derivatives of the four amino acids: alanine, tyrosine, glutamic acid (side-chain protected by an O-benzyl ester), and lysine (side-chain protected by trifluoroacetic acid amide).

Chemistry Assessment Section

The How Supplied section of the RLD labeling says:

"COPAXONE® Injection is supplied as a single-use pre-filled syringe containing 1.0 mL of a clear, colorless to slightly yellow, sterile, non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol, USP in cartons of 30 single-use pre-filled syringes, 33 alcohol preps (wipes) and instructions for use.

The recommended storage condition for the COPAXONE® Injection is refrigeration (2°C to 8°C / 36°F to 46°F). However, excursions from recommended storage conditions to room temperature conditions (15° to 30°C / 59° to 86° F) for up to one month have been shown to have no adverse impact on the product. Exposure to higher temperatures or intense light should be avoided."

B. Environmental Assessment Or Claim Of Categorical Exclusion

III. List Of Deficiencies To Be Communicated

See below.

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090218

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Glatiramer Acetate Injection, 20 mg/mL

This review has been focused on Section S.3.1 Elucidation of Structure, although some other sections have been partially reviewed. Review of other parts of the ANDA is continuing. Further deficiencies, if any, will be communicated separately.

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1.

(b) (4)

2.

3.

4.

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

(b) (4)

29.

30.

31.

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

2. An acceptable compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.

Sincerely,

{See appended electronic signature page.}

Paul Schwartz, Ph.D.
Acting Director,
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Chemistry Assessment Section: Chemistry Comments to be Provided to the Applicant

cc: ANDA 090218

Endorsements:

HFD-625/ELSchaefer, Chemist/

HFD-625/BCai, Team Leader/

HFD-617/EChuh, Project Manager/

V:\Chemistry Division I\Team 12\TL Folder\ANDA\Final\90218N00R02A_021411.doc

TYPE OF LETTER: NOT APPROVABLE - MAJOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EUGENE L SCHAEFER
02/14/2011

EUNJUNG E CHUH
02/14/2011

BING CAI
02/14/2011

ANDA 90-218

Glatiramer Acetate Injection

Sandoz Inc.

**Patricia M. Takahara, Ph.D.
Office of Generic Drugs
Immediate Office**

Table of Contents

The Executive Summary	6
I. Recommendations	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable	6
II. Summary of Chemistry Assessments	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used	8
C. Basis for Approvability or Not-Approval Recommendation	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q)	9
S. DRUG SUBSTANCE	9
S.1 General Information	9
S.2 Manufacture	10
S.3 Characterization	19
S.4 Control of Drug Substance	59
S.5 Reference Standards	62
S.6 Container Closure System	62
S.7 Stability	62
P. DRUG PRODUCT	62
P.1 Description and Composition of the Drug Product	63
P.2 Pharmaceutical Development	63
P.3 Manufacture	63
P.4 Control of Excipients	64
P.5 Control of Drug Product	64
P.6 Reference Standards	64
P.7 Container Closure System	64
P.8 Drug Product Stability	64
II. Administrative	65
A. Reviewer’s Signature	65
B. Endorsement Block	65
C. CC Block	65

Chemistry Review Data Sheet

1. ANDA 90-218
2. REVIEW #: 1
3. REVIEW DATE: September 5, 2008
4. REVIEWER: Patricia M. Takahara, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original Submission

Document Date
December 26, 2007

7. NAME & ADDRESS OF APPLICANT:

Name: Sandoz Inc.
506 Carnegie Center
Address: Suite 400
Princeton, NJ 08540
Representative: Srinivasa S. Rao
Director, Regulatory Affairs
Telephone: (609) 627-08885
Fax: (609) 395-2792

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Copaxone® (Reference Listed Drug)
- b) Non-Proprietary Name (USAN): Glatiramer Acetate Injection

9. LEGAL BASIS FOR SUBMISSION:

Chemistry Review Data Sheet

Sandoz Inc. (“Sandoz”), by this ANDA, is requesting approval for glatiramer acetate injection; 20 mg/mL (the “Sandoz Product”). Upon information and belief, Sandoz believes that Teva Pharmaceuticals (“Teva”) is the holder of NDA 20-622 for the Approved Listed Drug Product, Copaxone®.

10. PHARMACOL. CATEGORY: Immunomodulatory agent

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 20 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED: X Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See section S.1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	[REDACTED]	(b) (4)	7			Micro Issue
(b) (4)	III			7			(b) (4) not reviewed: secondary container closure system
(b) (4)	III				7		

Chemistry Review Data Sheet

		(b) (4)				
--	--	---------	--	--	--	--

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

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5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	Deferred		
Labeling	Pending		
Bioequivalence	Pending		
EA	Not Applicable		
Radiopharmaceutical	Not Applicable		

19. ORDER OF REVIEW

The application submission covered by this review was taken in the date order of receipt.

Yes No If no, explain reason(s) below:

The ANDA is being reviewed as a special project by the Office of Generic Drugs Science Team due to its complexity.

The Chemistry Review for ANDA 90-218

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable. The applicant has not provided sufficient evidence to demonstrate sameness of the generic glatiramer acetate as compared to Copaxone®. For this reason, review of other sections of the ANDA are being deferred.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not Applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Glatiramer acetate is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate synthesis reaction are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338 respectively. The purified drug product has an average molecular weight of 5000-9000 Da.

The peptide copolymers in the drug product range from about 40 to 100 amino acids in length and have been described as having “random” sequences. In fact, the sequences are not truly random but rather depend upon the coupling chemistry for the component amino acid monomers. The resultant drug product is, therefore, a mixture of peptide copolymers with defined composition, sequences, and physicochemical properties that are conserved from batch to batch during manufacturing.

Glatiramer acetate is an heterogeneous peptide copolymer that is produced by a well known process that has been published in patents and the literature.^{1,2} The synthesis of glatiramer acetate involves the polymerization of the N-carboxyanhydrides (NCAs) of

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² Teitelbaum D, Gan R, Meshorer A, Hirshfeld T, Arnon R, Sela M, inventors; Therapeutic Copolymer. US patent 3,849,550. 1974.

Executive Summary Section

the amino acids alanine, tyrosine, glutamic acid (γ -O-benzyl ester), and lysine (ϵ -trifluoroacetic acid amide).³ Steps in the polymerization of the NCA amino acids include (1) initiation, (2) propagation, and (3) termination. The polymerization steps are then followed by (4) depolymerization and (5) deprotection.

(b) (4)



(b) (4)



Executive Summary Section

(b) (4)



B. Description of How the Drug Product is Intended to be Used

Glatiramer acetate is a daily subcutaneous injection indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis (RRMS).

C. Basis for Approvability or Not-Approval Recommendation

Not Approvable. The applicant has not provided sufficient evidence to demonstrate sameness of the generic glatiramer acetate as compared to Copaxone®. For this reason, review of other sections of the ANDA is being deferred.

Chemistry Assessment Section

P.1 Description and Composition of the Drug Product

The formulation is Q1/Q2 to the RLD.

Ingredient	Sandoz	RLD
Glatiramer acetate	20 mg	20 mg
Mannitol	40 mg	40 mg
Water (pH 5.5-7.0)	1.0 mL	1.0 mL

P.2 Pharmaceutical Development

Review of this section is deferred at this time.

P.3 Manufacture

Who manufactures the drug product?

Name and Address	Responsibilities
(b) (4)	Manufactures drug product.
	Performs secondary packaging of drug product.
	Performs and/or may perform physical, chemical, and microbiological testing drug product for batch release and stability studies.
	Performs and/or may perform physical, chemical, and microbiological testing of drug

Chemistry Assessment Section

(b) (4)	product and excipients for batch release and stability studies.
	Performs and/or may perform chemical and bioassay testing of drug product for batch release and stability testing.

P.4 Control of Excipients

Review of this section is deferred at this time.

P.5 Control of Drug Product

Review of this section is deferred at this time.

P.6 Reference Standards

Review of this section is deferred at this time.

P.7 Container Closure System

Glatiramer acetate is a single-use pre-filled syringe containing 1.0 mL of a sterile non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol.

P.8 Drug Product Stability

Review of this section is deferred at this time.

II. Administrative

A. Reviewer's Signature

B. Endorsement Block

PTakahara/09-05-08

ARaw/09-05-08

MSmela/09-05-08

RPatel/09-05-08

C. CC Block

Chemistry Assessment Section

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-218 APPLICANT: Sandoz Inc.
DRUG PRODUCT: Glatiramer Acetate Injection

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. We have the following general comment with regard to the manufacture of the drug substance:

- a.  (b) (4)
- b. 

2. We have the following general comments with regard to the characterization of glatiramer acetate and the demonstration of sameness in Section 3.2.S.3:

- a.  (b) (4)
- b. 
- c. 

Chemistry Assessment Section

1. Please be advised that the review of the remainder of the CMC section of the application is deferred until the deficiencies of the information on drug substance sameness are fully resolved.
2. Your sterility assurance, bioequivalence, and labeling information are pending review. Deficiencies, if any, will be communicated separately.
3. We may require a satisfactory method validation study in an FDA laboratory to support the ANDA and will schedule it at an appropriate time.
4. An acceptable compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.

Sincerely,

{See appended electronic signature page.}

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Patricia Takahara
9/15/2008 01:12:57 PM
CHEMIST

Simon Eng
9/15/2008 01:40:35 PM
CSO

Michael Smela
9/15/2008 03:02:00 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 090218

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090218
Drug Product Name	Glatiramer Acetate Injection
Strength(s)	20 mg/mL
Applicant Name	Sandoz Inc.
Address	2555 West Midway Blvd. Broomfield, CO 80038-0446
Applicant's Point of Contact	Jean Domenico, Associate Director, Regulatory Affairs*
Contact's Telephone Number	303-438-4242
Contact's Fax Number	303-438-4600
Original Submission Date(s)	12/26/2007
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Santhosh K. Pabba, Ph.D.
OVERALL REVIEW RESULT	ADEQUATE
WAIVER REQUEST RESULT	ADEQUATE
OSIS INSPECTION RESULT	N/A

* – as per the 356h submitted on 03/16/2015

I. EXECUTIVE SUMMARY

This is an addendum to the previous bioequivalence (BE) review dated 10/21/2013 (Primary Review)¹.

Earlier, the Division of Bioequivalence I (DBI) considered whether the test product, Glatiramer Acetate Injection, 20 mg/mL, met the criteria set forth in Section 21 CFR § 320.22 (b)(1), which includes, in relevant part, requirements that the test product is a parenteral solution intended solely for administration by injection and that the test product and RLD contain the same active and inactive ingredients in the same concentration (i.e., that the active and inactive ingredients of the test product and RLD are qualitatively and quantitatively the same (Q1/Q2)). As noted in the Primary Review, DBI found that the test product met the foregoing requirements, subject to concurrent CMC review by the Office of Generic Drugs (OGD), Division of Chemistry (currently the Office of Pharmaceutical Quality) in addressing the evaluation of pharmaceutical equivalence of the Test and RLD product, including active ingredient sameness, which is a predicate to the above-mentioned requirement that the active ingredient of the test and RLD products be qualitatively the same. The finding in the Primary Review that the test product and RLD product are Q1/Q2 (subject to concurrent CMC review) incorporates a

¹ ANDA #090218, Division of Bioequivalence Review (10/21/2013)

finding that the test and RLD products contain the same inactive ingredients in the same concentration.² With respect to the active ingredients in the test and RLD products, the CMC review is now complete³ and found the test and RLD products to be pharmaceutically equivalent.⁴ Thus, the test and RLD products contain the same active ingredients in the same concentration. The CMC review also confirmed that the test product is a solution.⁵ Finally, the test product is a parenteral solution that is intended solely for administration by injection.⁶ Therefore, in light of the CMC review, DBI confirms that the requirements of Section 21 CFR § 320.22 (b)(1) are met and thus, the *in vivo* bioavailability/bioequivalence of the drug product is self-evident, and the requirement for the submission of data regarding the bioequivalence of the test product is waived. DBI has no further questions for the firm at this time.

The application is **adequate** with respect to bioequivalence testing.

² See Reference 1.

³ ANDA # 090218, CMC Review 5

⁴ “Pharmaceutical equivalents” is defined as “drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient . . . and meet the identical compendial or other applicable standard of identity, strength, quality, and purity” 21 CFR 320.1(c).

⁵ ANDA #090218, CMC Review 4, pages 77-85. Also see Reference 3.

⁶ ANDA #090218, Labeling Review (03/14/2014)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090218

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Glatiramer Acetate Injection 20 mg/mL

The Division of Bioequivalence I has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{ See appended electronic signature page }

Wayne I. DeHaven, Ph.D.
Acting Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Bing V.
Li -S

Digitally signed by Bing V. Li -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Bing V. Li -S,
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Date: 2015.04.15 16:56:37
-04'00'

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	090218
Drug Product Name	Glatiramer Acetate Injection
Strength(s)	20 mg/mL
Applicant Name	Sandoz Inc.
Address	506 Carnegie Center Suite 400 Princeton, NJ 08540
Applicant's Point of Contact	Srinivasa S. Rao, Pharm.D., Director, Regulatory Affairs
Contact's Telephone Number	609-627-8885
Contact's Fax Number	609-395-2792
Original Submission Date(s)	12/26/2007
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Santhosh K. Pabba, Ph.D.
OVERALL REVIEW RESULT	ADEQUATE (WITH RESPECT TO BIOEQUIVALENCE)
WAIVER REQUEST RESULT	ADEQUATE (WITH RESPECT TO BIOEQUIVALENCE)
DSI INSPECTION RESULT	N/A

1 EXECUTIVE SUMMARY

The firm has requested a waiver of *in vivo* bioequivalence (BE) study requirements under Section 21 Code of Federal Regulations (CFR) § 320.22 (b)(1) for its product, Glatiramer Acetate Injection, 20 mg/mL. The reference-listed drug (RLD) product is Copaxone® (glatiramer acetate) Injection, 20 mg/mL by Teva Pharmaceuticals Inc., and approved on December 20, 1996 under NDA # 20622.

The Division of Bioequivalence I (DBI) considers that the test product, Glatiramer Acetate Injection, 20 mg/mL, meets the criteria set forth in Section 21 CFR § 320.22 (b) (1). However, the DBI defers to the Office of Generic Drugs (OGD), Division of Chemistry in addressing the evaluation of pharmaceutical equivalence of the Test and RLD product, which is still pending, see Section 4.2. Therefore, the DBI has no further question for the firm at this time.

The application is **adequate** with respect to bioequivalence testing.

2 TABLE OF CONTENTS

1	Executive Summary	1
2	Table of Contents	2
3	Submission Summary.....	3
3.1	Drug Product Information	3
3.2	PK/PD Information ,	3
3.3	OGD Recommendations for Drug Product	4
3.4	Contents of Submission.....	6
3.5	Formulation	6
3.6	Waiver Request(s).....	6
3.7	Deficiency Comments	7
3.8	Recommendations	7
3.9	Comments for Other OGD Disciplines	7
4	Appendix	8
4.1	Formulation Data	8
4.2	Overall Reviewer’s Comments:	10
4.3	Consult Review	11
4.4	OGD Science Staff Review on Glatiramer Acetate Injection (Control # 13-0444)	11
4.5	Attachments (Draft Guidance not yet published).....	12
4.6	Additional Attachments	14
4.7	Outcome Page	17

3 SUBMISSION SUMMARY

3.1 Drug Product Information ¹

Test Product	Glatiramer Acetate Injection, 20 mg/mL
Reference Product	Copaxone® (glatiramer acetate) solution for subcutaneous injection, 20 mg/mL
RLD Manufacturer	Teva Pharmaceuticals Inc.
NDA No.	020622
RLD Approval Date	December 20, 1996
Indication	For reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis, (b) (4)

3.2 PK/PD Information ^{2, 3}

Bioavailability	Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Larger fragments of glatiramer acetate can be recognized by glatiramer acetate-reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some may enter the systemic circulation intact.
Food Effect	N/A
T_{max}	T _{max} ranges from 1.2 – 2.5 hours.
Metabolism	Hydrolyzed by proteases ⁴ . A substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally.
Excretion	Animal studies showed that the peptides break into small peptide fragments and amino acids which subsequently incorporated into endogenous polypeptides and proteins. 47 – 57% of radioactivity is excreted into urine within 48 hours after s.c. injection of ¹²⁵ I labeled copolymer-1 to rats. The clearance of the total radiolabel averaged 65±8 mL/h/kg in rats.
Half-life	N/A
Drug Specific Issues (if any)	<i>Subcutaneous use only. Do not administer intravenously.</i>

N/A: Not applicable and/or mentioned in the RLD labeling.

Furthermore, this product is given subcutaneously as an injection as is hydrolyzed locally; therefore, some of the PK properties of the drug product may not easily be determined and/or negligible.

¹ Drugs@fda database, link:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>

² Drugs@fda database, link: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020622s0871b1.pdf

³ Ibrahim S., NDA 20622 Biopharmaceutical Review Jan 29, 1996

⁴ Database: Drugbank, link: <http://www.drugbank.ca/drugs/DB05259>

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	N/A – Waiver Request
Analytes to measure (in plasma/serum/blood):	N/A
Bioequivalence based on:	<p>Reviewer note: Please see the Draft Guidance on glatiramer acetate in the Section: 4.5 for complete details (Draft Guidance obtained from the Science Team review of Control # 13-0444 in the RFS database on September 19, 2013). Please note that the draft guidance on glatiramer acetate is not yet published as of the date of the current review.</p> <p>When the test and the reference listed drug (RLD) products</p> <ul style="list-style-type: none"> • have the same active ingredient by demonstrating equivalent characteristics of the active ingredient, and • have qualitatively (Q1) and quantitatively (Q2) the same drug product formulation <p><i>In vivo</i> bioequivalence study can be waived</p> <hr/> <p>Additional information</p> <p><i>Scientific Rationale for Waiver of In Vivo Bioequivalence Studies:</i> Glatiramer acetate injection is a parenteral solution intended solely for subcutaneous injection. According to 21 CFR 320.22, bioequivalence is accepted as "self-evident" if a drug product contains the same active and inactive ingredients in the same concentration as RLD and when the drug product is a parenteral solution intended solely for administration by injection. Hence, if a test drug product has the same active ingredient as the RLD and is Q1/Q2 with the RLD, <i>in vivo</i> bioequivalence studies of glatiramer acetate injection can be waived.</p> <p>As part of the evaluation of pharmaceutical equivalence, confirmation that glatiramer acetate is a thermodynamically reversible solution eligible for a biowaiver is recommended to include:</p> <ol style="list-style-type: none"> 1. Size Distribution and Relative Abundance of Glatiramer Acetate Aggregates Design: at least three lots of both test and RLD products <p>Parameters to measure: D₁₀, D₅₀, D₉₀ of aggregates and the relative abundance of glatiramer acetate</p>

unimer and aggregates

2. Thermodynamic Reversibility of Glatiramer Acetate Aggregates

Design: at least three lots of both test and RLD products

Parameters to measure: D_{50} of aggregates and the relative abundance of glatiramer acetate unimer and aggregates upon dilution or temperature changes

Additional characterization assays are required to demonstrate the active ingredient sameness and formulation sameness between test drug product and RLD.

Same Active Ingredient: Additional in vitro and in vivo characterization studies are recommended to demonstrate the active ingredient sameness between the test and RLD products by demonstrating equivalent starting materials and basic chemistry, equivalent physicochemical properties, equivalent structural signatures of process (polymerization, depolymerization, and purification), and equivalent biological and immunological properties of the peptide copolymers. The characterization tests are recommended to be conducted on three batches of the test and RLD products (at least one ANDA batch should be produced by the commercial scale process).

Same Drug Product Formulation: To waive in vivo BE study, an applicant of a generic glatiramer acetate injection must demonstrate qualitative and quantitative sameness in active ingredient (glatiramer acetate 20 mg/mL), inactive ingredient (mannitol 40 mg/mL, pH 5.5-7.0) between the test drug product and RLD.

Impurity levels in the test product comparable to or lower than those found in the RLD: Generic applicants are recommended to demonstrate impurity levels in the test product comparable to or lower than those found in the RLD. The impurities in glatiramer acetate injection include process related impurities, aggregates of glatiramer acetate peptides, and leachates from the container closure system.

Summary of OGD or DBI History (for draft guidance not yet published see Section: 4.4):	(b) (4)
	<p>OGD has ten open controls (for glatiramer acetate injection. Among them, eight controls (03-959, 06-0294, 06-1110, 07-0816, 08-0205, 08-0399, 08-0681, and 11-0804) request guidance regarding bioequivalence study requirements. (b) (4)</p> <p>. Another control (13-0444) is an internal request by OGD for the BE recommendation. In addition, there are four closed citizen petition from the NDA sponsor requesting the agency not approve or accept any filings or ANDA's for generic of Copaxone (Docket No. FDA-2008-P-0529, FDA-2009-P-0555, FDA-2010-P-0642 and FDA-2012-P-0555).</p> <p>Please note that there are no protocols submitted for the current drug product. There are no control documents or protocols submitted by the current firm (Sandoz) for glatiramer acetate.</p>

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	--
Single-dose fed	No	--
Steady-state	No	--
In vitro dissolution	No	--
Waiver requests	Yes	1
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	No	--
Amendments	No	--

3.5 Formulation

Location in appendix	Section 4.1
If a tablet, is the RLD scored?	N/A
If a tablet, is the test product biobatch scored	N/A
Is the formulation acceptable?	Acceptable from DBI perspective. However, the DBI defers to the OGD, Division of Chemistry in addressing the evaluation of pharmaceutical equivalence of the Test and RLD product
If not acceptable, why?	N/A

3.6 Waiver Request(s)

Strengths for which waivers are requested	20 mg/mL
Proportional to strength tested in vivo?	N/A

Is dissolution acceptable?	N/A
Waivers granted?	Yes (Based on the bioequivalence testing requirements set forth in 21 CFR 320.22(b)(1))
If not then why?	The Division of Chemistry will address pharmaceutical equivalence of the test and reference product.

3.7 Deficiency Comments

None

3.8 Recommendations

1. The DBI agrees that the information submitted by Sandoz Inc., demonstrates that the test product, Glatiramer Acetate Injection, 20 mg/mL, meets the requirements of Section 21 CFR § 320.22 (b) (1). Accordingly *in vivo* bioequivalence testing should not be undertaken.
2. The OGD, Division of Chemistry is currently evaluating the pharmaceutical equivalence of the Test and RLD product. Therefore, the DBI has no further question for the firm at this time.

The application is **adequate** with respect to the bioequivalence testing of the drug product.

3.9 Comments for Other OGD Disciplines

Discipline	Comment
Chemistry	The DBI defers to the Division of Chemistry in addressing the evaluation of pharmaceutical equivalence of the Test and RLD product.

4 APPENDIX

4.1 Formulation Data

(NOT FOR RELEASE UNDER FOIA)

4.1.1 Formulation Data of the Test Product ⁵

Component	Amount per Syringe	Function	Quality Standard
Glatiramer Acetate	20 mg	Drug Substance	In-house
Mannitol	40 mg	(b) (4)	USP, EP
Water for Injection (pH 5.5-7.0)	q.s. to 1 mL	(b) (4)	USP

Reviewer note: the pH of the exhibit batch # CT0743 is (b) (4). The pH of the test product is within the acceptance criteria of (b) (4).

Based on the Chemistry review⁶ for the current ANDA, Glatiramer Acetate, the active ingredient (test lot # 077K7277), consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of (b) (4) respectively. The average molecular weight of Glatiramer Acetate is (b) (4) Daltons.

⁵ EDR ANDA 090218 Module 3.2.P.1.

⁶ DARRTS, ANDA # 090218, TAKAHARA, PATRICIA M 09/15/2008 N/A 09/15/2008 REV-QUALITY-03(General Review) Original-1 Archive

4.1.2 Formulation Data of the Reference Listed Product (RLD)⁷

The formulation of the RLD product, Copaxone®, is listed as follows.

Composition of Copaxone Pre-filled Syringe

Component	Quality Standard	Amount per Syringe	Amount per ^{(b) (4)} Batch	Amount per ^{(b) (4)} Batch
Glatiramer Acetate	Teva/Approved	20 mg		^{(b) (4)}
Mannitol	NDA USP and EP	40 mg		
Water for Injection	USP and EP	q.s. to 1 mL		

^{(b) (4)}

As per the RLD label², Glatiramer Acetate, the active ingredient of COPAXONE, consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5,000 – 9,000 Daltons. Glatiramer Acetate is identified by specific antibodies. Chemically, Glatiramer Acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

(Glu, Ala, Lys, Tyr)_x • xCH₃COOH
 (C₅H₉NO₄•C₃H₇NO₂•C₆H₁₄N₂O₂•C₉H₁₁NO₃)_x • xC₂H₄O₂
 CAS - 147245-92-9

COPAXONE is a clear, colorless to slightly yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 1 mL of solution contains 20 mg of Glatiramer Acetate and 40 mg of mannitol (please note that COPAXONE is supplied as a single-use prefilled syringe). The pH range of the solution is approximately 5.5 to 7.0.

Is there an overage of the active pharmaceutical ingredient (API)?	NO ⁸
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	The DBI defers to the Division of Chemistry in addressing the evaluation of pharmaceutical equivalence of the Test and Reference products.

⁷ DARRTS, NDA # 020622, HEIMANN, MARTHA R 08/23/2001 N/A 08/23/2001 REV-QUALITY-03(General Review) Supplement-23 (Manufacturing (CMC)) Archive .

⁸ ANDA# 090218, Module: 2.3.P (Quality Overall Summary), submission date: 12/27/2007.

4.2 Overall Reviewer's Comments:

1. The test and RLD products are Q1 (qualitatively) and Q2 (quantitatively) same.
2. The pH is comparable between the test (b)(4) and the RLD (5.5 to 7.0). The firm provided the pH data for the test (exhibit lot # CT0743)⁹. Please see the Certificate of Analysis (COA) of the test product in Section: 4.6.

Acceptance Criterion	(b)(4)	
Summary of Justification	The acceptance criterion is based on the pH range of the reference listed drug (5.5 to 7.0). Therefore the pH range of Glatiramer Acetate Injection is established as (b)(4)	
Data for Lots	Lot CT0743	Lot CT0750
pH of drug product	7.0	6.2

The active ingredient sameness is critical for ensuring that a proposed generic Glatiramer Acetate product is therapeutically equivalent to Copaxone®. The DBI defers to the Division of Chemistry in addressing the evaluation of pharmaceutical equivalence of the Test and RLD product (please refer to Section: 4.4 for draft guidance developed by Science Team at OGD for additional information, please note that the draft guidance on glatiramer acetate is not yet published).

3. The Division of Bioequivalence (DBI) considers the test product, Glatiramer Acetate Injection, 20 mg/mL, meets the criteria set forth in Section 21 CFR § 320.22 (b) (1). However, the DBI defers to the OGD, Division of Chemistry in addressing the evaluation of pharmaceutical equivalence of the Test and RLD product. Therefore, the DBI has no further question for the firm at this time.

Therefore, the overall review result for this application is **adequate** with respect to the bioequivalence testing requirements.

⁹ EDR, ANDA # 090218, Module: 3.2.P.5.4 (Batch Analyses) and Module: 3.2.P.5.6 (Justification of Specifications), submission date: December 27, 2007.

4.3 Consult Review

None.

4.4 OGD Science Staff Review on Glatiramer Acetate Injection (Control # 13-0444)

Please refer to the following document for details of the review on Glatiramer Acetate Injection (Control # 13-0444).

Link: V:\Science Group\MASTER Files BE Posting\glatiramer_acetate_inj_020622\
glatiramer_acetate_inj_020622.doc

4.5 Attachments (Draft Guidance not yet published)

Active ingredient:	Glatiramer Acetate
Form/Route:	Injection/Subcutaneous
Recommended studies:	Waiver of in vivo bioequivalence

When the test and the reference listed drug (RLD) products

- have the same active ingredient by demonstrating equivalent characteristics of the active ingredient, and
- have qualitatively (Q1) and quantitatively (Q2) the same drug product formulation

In vivo bioequivalence study can be waived

Additional information

Scientific Rationale for Waiver of In Vivo Bioequivalence Studies: Glatiramer acetate injection is a parenteral solution intended solely for subcutaneous injection. According to 21 CFR 320.22, bioequivalence is accepted as "self-evident" if a drug product contains the same active and inactive ingredients in the same concentration as RLD and when the drug product is a parenteral solution intended solely for administration by injection. Hence, if a test drug product has the same active ingredient as the RLD and is Q1/Q2 with the RLD, *in vivo* bioequivalence studies of glatiramer acetate injection can be waived.

As part of the evaluation of pharmaceutical equivalence, confirmation that glatiramer acetate is a thermodynamically reversible solution eligible for a biowaiver is recommended to include:

1. Size Distribution and Relative Abundance of Glatiramer Acetate Aggregates

Design: at least three lots of both test and RLD products

Parameters to measure: D_{10} , D_{50} , D_{90} of aggregates and the relative abundance of glatiramer acetate unimer and aggregates

2. Thermodynamic Reversibility of Glatiramer Acetate Aggregates

Design: at least three lots of both test and RLD products

Parameters to measure: D_{50} of aggregates and the relative abundance of glatiramer acetate unimer and aggregates upon dilution or temperature changes

Additional characterization assays are required to demonstrate the active ingredient sameness and formulation sameness between test drug product and RLD.

Same Active Ingredient: Additional in vitro and in vivo characterization studies are recommended to demonstrate the active ingredient sameness between the test and RLD products by demonstrating equivalent *starting materials and basic chemistry*, equivalent *physicochemical properties*, equivalent *structural signatures of process (polymerization, depolymerization, and purification)*, and equivalent *biological and immunological properties* of the peptide copolymers.

The characterization tests are recommended to be conducted on three batches of the test and RLD products (at least one ANDA batch should be produced by the commercial scale process).

Same Drug Product Formulation: To waive in vivo BE study, an applicant of a generic glatiramer acetate injection must demonstrate qualitative and quantitative sameness in active ingredient (glatiramer acetate 20 mg/mL), inactive ingredient (mannitol 40 mg/mL, pH 5.5-7.0) between the test drug product and RLD.

Impurity levels in the test product comparable to or lower than those found in the RLD: Generic applicants are recommended to demonstrate impurity levels in the test product comparable to or lower than those found in the RLD. The impurities in glatiramer acetate injection include *process related impurities, aggregates of glatiramer acetate peptides, and leachates from the container closure system.*

Following this page, 2 pages withheld in full - (b)(4)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090218

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Glatiramer Acetate Injection 20 mg/mL

The Division of Bioequivalence I has completed its review and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are comprehensive as of issuance. These comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.7 Outcome Page

ANDA: 090218

Reviewer: Pabba, Santhosh

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Glatiramer Acetate Injection

Productivity:

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
14704	12/26/2007	Other	Waiver Injectable	1	1
				Bean Total:	1

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/s/

SANTHOSH K PABBA
10/16/2013

UTPAL M MUNSHI
10/18/2013

HOAINHON N CARAMENICO
10/21/2013

HOAINHON N CARAMENICO on behalf of DALE P CONNER
10/21/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 090218

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

March 31, 2014

ANDA: 090218

Drug Product Name

Proprietary: N/A

Non-proprietary: Glatiramer Acetate

Drug Product Priority Classification: N/A

Review Number: # 4

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
2/28/14	2/28/14	N/A	3/5/14

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
12/11/13*	3	8/28/13
1/30/13**		
10/26/12**		
4/30/10	2	05/18/10
12/26/07	1	12/15/08

* Stated as 12/12/13 in GSR; ** Telephone Amendment; *** Gratuitous Amendment dated 10/29/12 in GSR.

Applicant/Sponsor

Name: Sandoz, Inc.

Address: 2555 West Midway Blvd., P. O. Box 446, Broomfield, CO 80038-0446.

Representative: Jean Domenico

Telephone: 303-438-4242

Name of Reviewer: Dupeh Palmer, Ph.D.

Conclusion: This submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.**
- 1. TYPE OF SUBMISSION:** ANDA original amendment
 - 2. SUBMISSION PROVIDES FOR:** Response to Agency’s complete response deficiency letter, including microbiology deficiencies.
 - 3. MANUFACTURING SITE:**
Previously proposed: (b) (4)

Proposed Alternate site: Novartis Vaccines and Diagnostics, 475 Green Oaks Parkway Holly Springs, NC 27540.
 - 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 20mg/mL, sterile solution for subcutaneous injection. Supplied as a 1mL fill in a 1mL single-use glass syringe with a 29 Ga ½ inch fixed needle.
 - 5. METHOD(S) OF STERILIZATION:** (b) (4)
 - 6. PHARMACOLOGICAL CATEGORY:** Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis.

B. SUPPORTING/RELATED DOCUMENTS: (b) (4) Type III DMF (b) (4)
 _____, and associated reviews:
 (b) (4).doc dated 5/4/12 by J. Wells (adequate); (b) (4).doc dated 8/26/13 by H. Ngai (adequate); (b) (4).doc dated 8/28/13 and (b) (4).doc dated 3/26/14 by D. Palmer (adequate).

C. REMARKS: An E-CTD submission. The 2/28/14 submission contains the applicant’s responses to microbiology deficiencies conveyed in the Agency’s 2/14/14 Complete Response Deficiency Letter.

Filename: 090218a3.doc
 Template version: microtemplatectdqv9_OGD_2013v1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – The submission is recommended for approval on the basis of sterility assurance.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - The drug product will be manufactured in the (b)(4) manufacturing area of the Novartis Vaccines and Diagnostics manufacturing facility. Filling into 1mL (b)(4) Type 1 clear glass long barrel glass syringe is performed in (b)(4)
- B. Brief Description of Microbiology Deficiencies** – None identified.
- C. Assessment of Risk Due to Microbiology Deficiencies** – No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.
- D. Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/ Dupeh Palmer, Ph.D.
 Microbiology Team Leader/Jesse Wells, Ph.D.

C. CC Block
 cc: Field Copy

- ❖ [REDACTED] (b) (4)
- ❖ [REDACTED]

Note to Reviewer: [REDACTED] (b) (4)
[REDACTED]
[REDACTED] is followed; therefore the reviewer assumes that
the [REDACTED] (b) (4) guidelines therein are followed.

Acceptable

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/s/

DUPEH G Palmer-Ochieng
03/31/2014

SONG H KIM
03/31/2014

JESSE WELLS
03/31/2014

Product Quality Microbiology Review

January 28, 2014

ANDA: 090218

Drug Product Name

Proprietary: N/A

Non-proprietary: Glatiramer Acetate

Drug Product Priority Classification: N/A

Review Number: # 3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/11/13*	12/12/13		1/16/14
1/30/13**	1/30/13	N/A	8/1/13
10/26/12***	10/29/12		

* Stated as 12/12/13 in GSR; ** Telephone Amendment; *** Gratuitous Amendment dated 10/29/12 in GSR.

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
4/30/10	2	5/18/10
12/26/07	1	12/15/08

Applicant/Sponsor

Name: Sandoz, Inc.

Address: 2555 West Midway Blvd., P. O. Box 446, Broomfield, CO
80038-0446.

Representative: Jean Domenico

Telephone: 303-438-4242

Name of Reviewer: Dupeh Palmer, Ph.D.

Conclusion: This submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A. 1. TYPE OF SUBMISSION:** ANDA original gratuitous amendment
- 2. SUBMISSION PROVIDES FOR:** Gratuitous information regarding the use of alternate manufacturing site for the drug product, and telephone amendment regarding replacement of the product's (b) (4) Ga ½ inch syringe needle with a 29 Ga ½ inch syringe needle.
- 3. MANUFACTURING SITE:**
Previously reviewed site: (b) (4)
Proposed Alternate site: Novartis Vaccines and Diagnostics, 475 Green Oaks Parkway Holly Springs, NC 27540.
- 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 20mg/mL, sterile solution for subcutaneous injection. Supplied as a 1mL fill in a 1mL single-use glass syringe with a 29 Ga ½ inch fixed needle.
- 5. METHOD(S) OF STERILIZATION:** (b) (4)
- 6. PHARMACOLOGICAL CATEGORY:** Reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis.
- B. SUPPORTING/RELATED DOCUMENTS:** (b) (4) Type III DMF (b) (4), and associated reviews: (b) (4).doc dated 5/4/12 by J. Wells (adequate); (b) (4).doc dated 8/26/13 by H. Ngai (adequate), (b) (4).doc dated 8/23/13 by D. Palmer (adequate), and (b) (4).doc dated 8/28/13 by D. Palmer (review pending adequate).
- C. REMARKS:** An E-CTD submission. The 10/26/12 submission is a gratuitous amendment pertaining to the use of Novartis Vaccines and Diagnostics, Holly Springs, NC, as an alternate site for manufacturing of the drug product in addition to the previously reviewed site (b) (4) site located in (b) (4). The 1/30/13 telephone amendment confirms replacement of the drug product's (b) (4) (b) (4) Ga ½ inch syringe needle with a 29 Ga ½ inch syringe needle, and was submitted in response to a 1/25/12 T-con between Ted Garnett (microbiology reviewer for the ANDA submission proposing the (b) (4) site), and Jean Domenico (Sandoz). Updated labeling information is provided in the 12/11/13 amendment submitted in response to CMC and labeling deficiencies.

Filename: 090218a2.doc
 Template version: microtemplatectdqv9_OGD_2013v1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This submission is **not recommended** for approval on the basis of sterility assurance.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - (b) (4)
 [Redacted]
- B. Brief Description of Microbiology Deficiencies** – DMF (b) (4) is deficient. Questions regarding: (b) (4)
 [Redacted] validation studies. (b) (4) test validation data are requested. Validation data for the (b) (4) process is requested
- C. Assessment of Risk Due to Microbiology Deficiencies** – The safety risk associated with the microbiology deficiencies is considered moderate.
- D. Contains Potential Precedent Decision(s)**- Yes No

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/ Dupeh Palmer, Ph.D.
 Microbiology Team Leader/Marla Stevens-Riley, Ph.D.

C. CC Block
 cc: Field Copy

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 090218 APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Glatiramer Acetate

The following deficiencies listed below may be delivered via the easily correctable deficiency method (10 day firm response expected) if the situation allows YES NO

Microbiology Deficiencies:

1. DMF (b) (4) is deficient. The DMF holder has been notified.

2. [Redacted] (b) (4)

3. [Redacted]

4. Regarding the (b) (4) used in production:
 - a) It is stated in this amendment that the production (b) (4)
[Redacted] Please explain the difference in the (b) (4)
(b) (4).

 - b) It is stated in the submission that (b) (4)
[Redacted]
[Redacted] testing during commercial production of the drug product.

5. It is noted that during the (b) (4)
[Redacted]

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/s/

DUPEH G Palmer-Ochieng
01/28/2014

SONG H KIM on behalf of CRAIG P KIESTER
01/30/2014

MARLA K STEVENS RILEY
01/30/2014

Product Quality Microbiology Review

May 18, 2010

ANDA: 090218

Drug Product Name

Proprietary: N/A

Non-proprietary: Glatiramer Acetate Injection

Drug Product Priority Classification: N/A

Review Number: 2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
04/30/2010	05/03/2010	N/A	05/04/2010

Submission History (for amendments only): N/A

Submission Date(s)	Microbiology Review #	Review Date(s)
12/26/2007	1	12/15/2008

Applicant/Sponsor

Name: Sandoz, Inc.

Address: 506 Carnegie Center, Suite 400, Princeton, NJ

Representative: Marcy MacDonald, Director of Regulatory Affairs

Telephone: 303-438-4599

Name of Reviewer: Theodore Garnett, Ph.D.

Conclusion: This submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.**
1. **TYPE OF SUBMISSION:** Original Amendment
 2. **SUBMISSION PROVIDES FOR:** Response to microbiology deficiencies; information supporting (b) (4) as the new commercial manufacturing site for Glatiramer Acetate Injection
 3. **MANUFACTURING SITE:**
(b) (4)
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Glatiramer acetate injection, 20 mg/mL, is a sterile solution intended for subcutaneous injection. It is supplied as a 1 mL fill in a 1 mL single-use glass syringe with a (b) (4) Ga ½ inch fixed needle.
 5. **METHOD(S) OF STERILIZATION:** (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis.
- B.** **SUPPORTING/RELATED DOCUMENTS:** (b) (4) Type III DMF (b) (4) and DMF reviews (b) (4).doc (dated March 14, 2007) and (b) (4).doc (dated June 25, 2007) by P. Dexter and (b) (4).doc (dated January 18, 2008) M. Stevens-Riley.
- C.** **REMARKS:** 1) This is an electronic application. 2) On July 13, 2009 Sandoz notified the FDA that manufacturing of Glatiramer Acetate Injection would be discontinued at (b) (4) and that all future Drug Product would be manufactured at (b) (4). In addition to the responses to the microbiology deficiencies arising from the original submission, the current amendment contains sterility assurance information supporting (b) (4) as a commercial manufacturing site for Glatiramer Acetate Injection. 3) A T-con was held with the applicant on 7/8/2010 to request information regarding actions taken when monitoring limits are exceeded. The applicant responded by e-mail on 7/14/2010 and the responses were incorporated into this review. A record of the T-con is saved in 090218a1microT-con07-08-2010.doc.

filename: 090218a1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This submission is **recommended** for approval on the basis of sterility assurance.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - (b) (4)
- B. Brief Description of Microbiology Deficiencies** – None identified.
- C. Assessment of Risk Due to Microbiology Deficiencies** – No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Microbiologist /Theodore Garnett, Ph.D.
Microbiology Team Leader/Lynne Ensor, Ph.D.
- C. CC Block**
cc: Field Copy

R.1 Executed Batch Record

Product lot # CL9-412 was manufactured in support of the application.

The batch records confirm that validated (b) (4)

(b) (4) manufacturing processes were used for the manufacture of each exhibit batch.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)****MODULE 1****A. PACKAGE INSERT**

Glatiramer acetate injection, 20 mg/mL, is a sterile solution intended for subcutaneous injection. It is supplied as a 1 mL fill in a 1 mL single-use glass syringe with a (b) (4) Ga ½ inch fixed needle. The storage temperature for Glatiramer acetate injection is 2 - 8°C (36 - 46°C).

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/s/

THEODORE O GARNETT
10/14/2010

ELIZABETH T MCNEAL
10/14/2010

Checked file and submission link. Both correct.

LYNNE A ENSOR
10/15/2010

Product Quality Microbiology Review

December 15, 2008

ANDA: 90-218

Drug Product Name

Proprietary: N/A

Non-proprietary: Glatiramer Acetate Injection

Drug Product Priority Classification: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
12/26/2007	12/27/2007	N/A	12/12/08

Submission History (for amendments only): N/A

Applicant/Sponsor

Name: Sandoz, Inc.

Address: 506 Carnegie Center, Suite 400, Princeton, NJ

Representative: Srinivasa S. Rao, Pharm. D., Director, Regulatory Affairs

Telephone: 609-627-8500 (General)

Name of Reviewer: Theodore Garnett, Ph.D.

Conclusion: This submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.**
1. **TYPE OF SUBMISSION:** Original ANDA
 2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product.
 3. **MANUFACTURING SITE:**

(b) (4)
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Glatiramer acetate injection, 20 mg/mL, is a sterile solution intended for subcutaneous injection. It is supplied as a 1 mL fill in a 1 mL single-use glass syringe with a (b) (4) Ga ½ inch fixed needle.
 5. **METHOD(S) OF STERILIZATION:**

(b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis.
- B.** **SUPPORTING/RELATED DOCUMENTS:**

(b) (4)

 Type III DMF

(b) (4)

 and DMF reviews

(b) (4)

.doc
(dated March 14, 2007) and

(b) (4)

.doc (dated June 25, 2007) by P. Dexter
and

(b) (4)

.doc (dated January 18, 2008) M. Stevens-Riley.
- C.** **REMARKS:** This is an electronic application.

filename: 90-218.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the “Product Quality Microbiology Assessment” and “List of Microbiology Deficiencies and Comments” sections.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** - (b) (4)
 (b) (4)
- B. Brief Description of Microbiology Deficiencies** – The deficiencies pertain to (b) (4)
 (b) (4)
- C. Assessment of Risk Due to Microbiology Deficiencies** – The safety risk associated with the microbiology deficiencies is considered low to moderate.

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
 Microbiologist /Theodore Garnett, Ph.D.
 Microbiology Team Leader/Lynne Ensor, Ph.D.
- C. CC Block**
 cc: Field Copy

N/A

R REGIONAL INFORMATION

R.1 Executed Batch Record

Product lot # CT0743 was manufactured in support of the application.

The batch records confirm that validated (b) (4) (b) (4) manufacturing processes were used for the manufacture of each exhibit batch.

**2. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)**

MODULE 1

A. PACKAGE INSERT

Glatiramer acetate injection, 20 mg/mL, is a sterile solution intended for subcutaneous injection. It is supplied as a 1 mL fill in a 1 mL single-use glass syringe with a (b) (4) Ga ½ inch fixed needle. The storage temperature for Glatiramer acetate injection is 2 - 8°C (36 - 46°C).

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 90-218 APPLICANT: Sandoz, Inc.

DRUG PRODUCT: Glatiramer Acetate Injection

Microbiology Deficiencies:

1.  (b) (4)
- 2.
- 3.
- 4.
- 5.

Please clearly identify your amendment to this facsimile as “RESPONSE TO MICROBIOLOGY DEFICIENCIES”. The “RESPONSE TO MICROBIOLOGY DEFICIENCIES” should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Theodore O Garnett
3/11/2009 09:11:08 AM
MICROBIOLOGIST

Bonnie McNeal
3/11/2009 11:48:38 AM
MICROBIOLOGIST
Checked for correct file and submission link. Both ok.

Lynne Ensor
3/11/2009 12:18:28 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 090218

OTHER REVIEWS

Copaxone Follow-up Discussion DARS Consult

7 July 2014

Division of Applied Regulatory Science
Office of Clinical Pharmacology

DARS Consult No: 2014-0927

1. Evaluate the data quality, sample variability (including method and batch to batch variability) and analytics and statistics used by TEVA on their gene expression studies related to comparing RLD Copaxone to generics.
 - a) Study design
 - b) Data quality
 - c) Data analysis and interpretation

2. Are comparative data from these sorts of studies valuable to the assessment of sameness for generic Copaxones?
 - a) Are there any reliable differences between the RLD batches and generic samples in individual gene expression or pathways in the TEVA studies?
 - b) Are any of the differences biologically plausible as relevant to product safety of efficacy (with OGD & OBP)
 - c) If the answer to both (a) and (b) is yes, is there a feasible and robust experimental approach to test generic candidate products

3. ADDED: Please comment on the relevance and validity of using the gene expression experiment to correlate to the clinical effects of GA

Study Design Comparison

Teva (b) (4)

Inject Mice with GA

↓ 3 Days

Prepare total spleen leukocytes
Analyze by microarray

Sample and Lot counts

Study	TEVA GA	Other GA
Teva	56/31*	11/5
(b) (4)		
Sandoz	16/4	17/8

*# samples / # lots

Sandoz/Momenta

Inject Mice with GA in Complete Freund's Adjuvant

↓ 11 Days

Remove Draining LN, prepare purified T-cells
Re-stimulate T-cells with GA + APC

↓ 2 Days

Wash out GA, feed

↓ 12 Days

Re-stimulate T-cells with GA + APC

↓ 1 Day

Analyze by microarray
(or cytokine release)

Study Design: Evaluation

	Teva (b) (4) studies	Sandoz/Momenta study
Clinical relevance of the model	Not clinically relevant	More clinically relevant
Time	Very early in primary response	2 nd re-stimulation after full primary response
Population	Mixed and uncharacterized spleen cells	Purified spleen T-cells
Sampling #s	Teva: unbalanced	Balanced
	(b) (4)	
External validation	None reported	Strongly Th2 biased cytokine production data (in ANDA files)
Technical and Lot Replicates:	Few or none	Few or none

Conclusion: Weaknesses in the Teva study design make it difficult to draw unambiguous conclusions about possible mechanisms and targets; However, the Sandoz study is considered to be more relevant and reliable

Microarray Data Quality

- Genome-scale microarrays are complex assays that generate high-dimensional data susceptible to technical bias that can mask true biological information (MIAME guidelines)

Evaluation

- The Teva study contained (a) significant bias in signal intensity from sample processing differences that obscured drug effects prior to statistical correction, and also (b) residual bias and high variability after statistical correction
- The effects attributed to generic GA by Teva were not repeatable (b) (4) in a study that minimized technical bias
- Quality evaluation of the Sandoz study data set was limited by the availability of only normalized data at this time. No issues were noted.
- **Conclusion**: The Teva microarray study is not appropriate for use in assessing claims of greater variability of generic drug batches or for biological interpretation of small-fold change differences between groups

Data Analysis & Interpretation

Evaluation

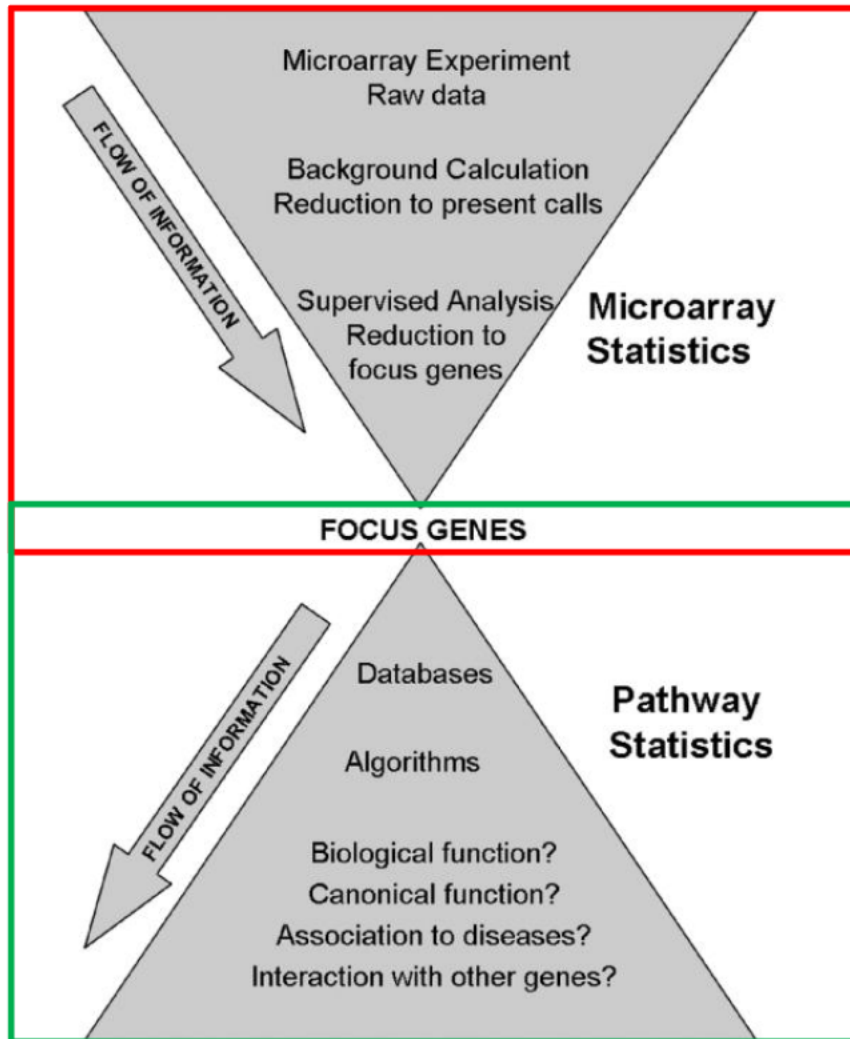
- Teva's claim of differences between RLD and generic is based on arbitrarily liberal statistical criteria and an arbitrarily selected subset of probes and/or samples
- When more widely used statistical criteria and a full set of probes/samples are used, no differences between RLD and generic were found
- DARS re-analysis of the microarray data sets generated in the (b) (4) (better controlled) and Sandoz (more relevant model) studies also revealed no biologically plausible differences between the generic products and RLD

Conclusion: Re-analysis of gene data in the Teva (b) (4) and Sandoz studies revealed no differences between the generic (b) (4) and Teva's glatiramer acetate product

Use of Microarray Data

- Product quality, data quality and biological relevance are critical to ensuring that microarray data can be reliably collected, analyzed and interpreted
- Basic requirements include:
 - Availability of product quality data for each of the drug lots used in the study and the contributions of lot variability to total experimental variability determined
 - Careful experimental design using a therapeutically relevant model
 - Adequate and balanced sampling
 - Use of the appropriate statistical methods
 - Clearly defined study endpoints related to specific genes and pathways relevant to the product's safety and efficacy
 - Confirmation by quantitative data obtained using additional assays
- **Conclusion**: microarray-derived gene expression data alone will be inconclusive but can be useful as part of the total evidence supporting an argument of equivalence or inequivalence

Microarray Data and Clinical Effects



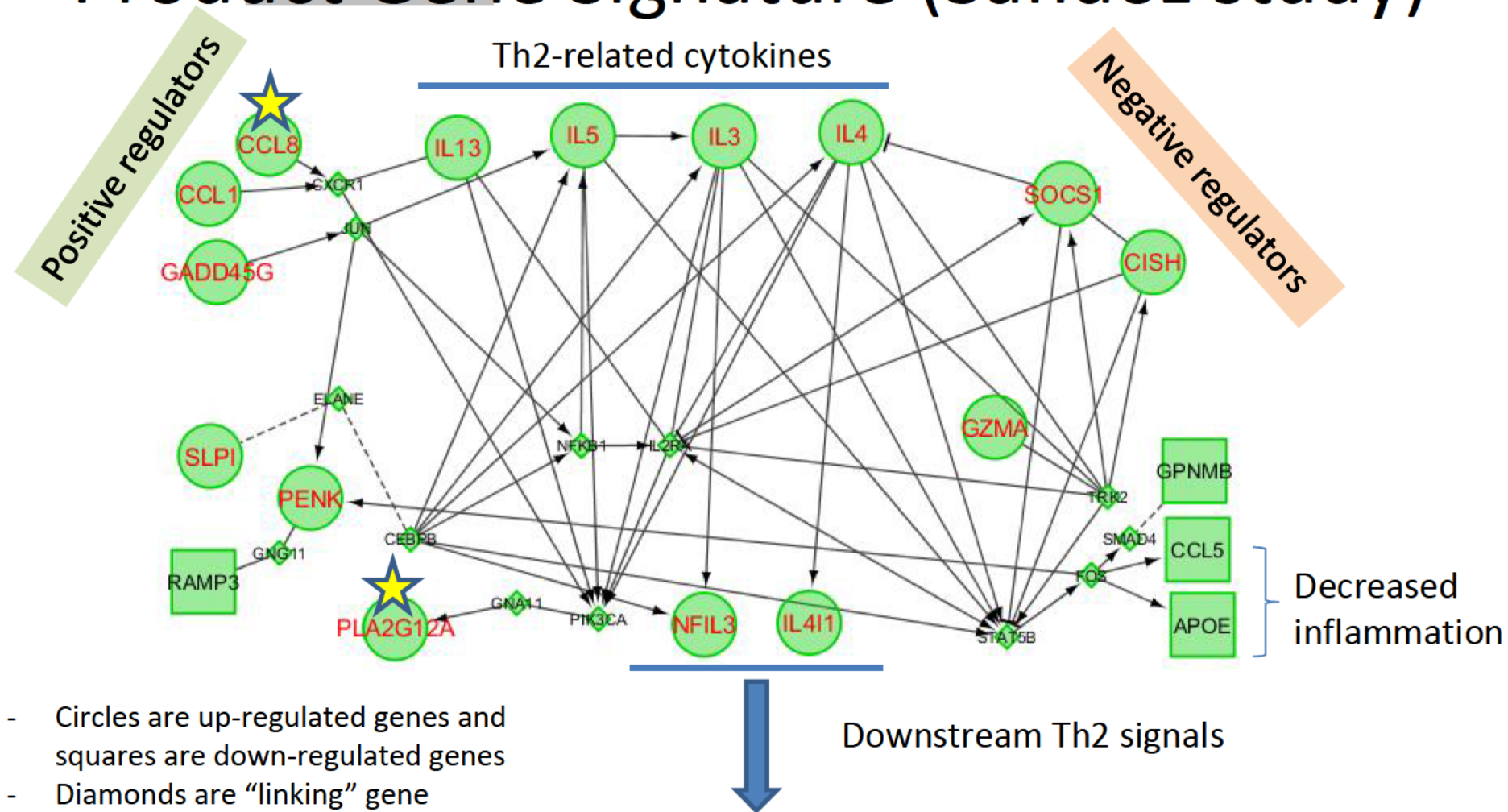
- No standard criterion in microarray data analysis to guide the assignment of gene “hits” to specific pathways
- Pathway databases are often incomplete and inconsistent
- Different pathway analytics may use different algorithms to determine linkages and network associations
- Pathway predictions using available systems are likely to be platform specific and not likely to identify the same mechanisms and networks
- Best approach includes a manual literature review step for confirmation

The first part of the graph depicts the multiple steps and entailed potential sources of bias while extracting the gene set of interest from a genome-wide microarray. The second part of the graph demonstrates the analytical steps in functional pathway analysis.

DARS Pathway Analysis

- A set of 29 Differentially Expressed Genes (DEGS) were identified as up- or down-regulated in T-cells by Copaxone® vs. medium in the Sandoz study using $P < 0.05$ and fold change > 4 as selection criteria
- A combination of Cytoscape and the Reactome databases were used together with a limited literature search to generate a “MOA” map of Copaxone® that includes 15 of the 29 genes.
- This map seems to tell a consistent story:
 - Th2-related cytokines (IL3, IL4, IL5, IL13) are up-regulated and they signal through some common pathway (STAT5B which is not up-regulated; NFIL3 and IL4I1 which are up-regulated) for downstream Th2 activities
 - Some genes (GADD45G and CCL1) are up-regulated to further increase Th2 cytokines
 - Other genes (SOC1 and CISH) are up-regulated as a negative regulators to counteract these cytokines.
 - Some genes (APOE and CCL5) are associated with Th2 signals and down-regulated for decreased antigen presentation and chemotaxis.
- **Conclusion: With some prior knowledge and appropriate study design, possible mechanisms of action may be identified and correlate with clinical effects (i.e. related to Th2 signals) using gene expression data**

Pathway Analysis of Sandoz and Teva Product Gene Signature (Sandoz study)

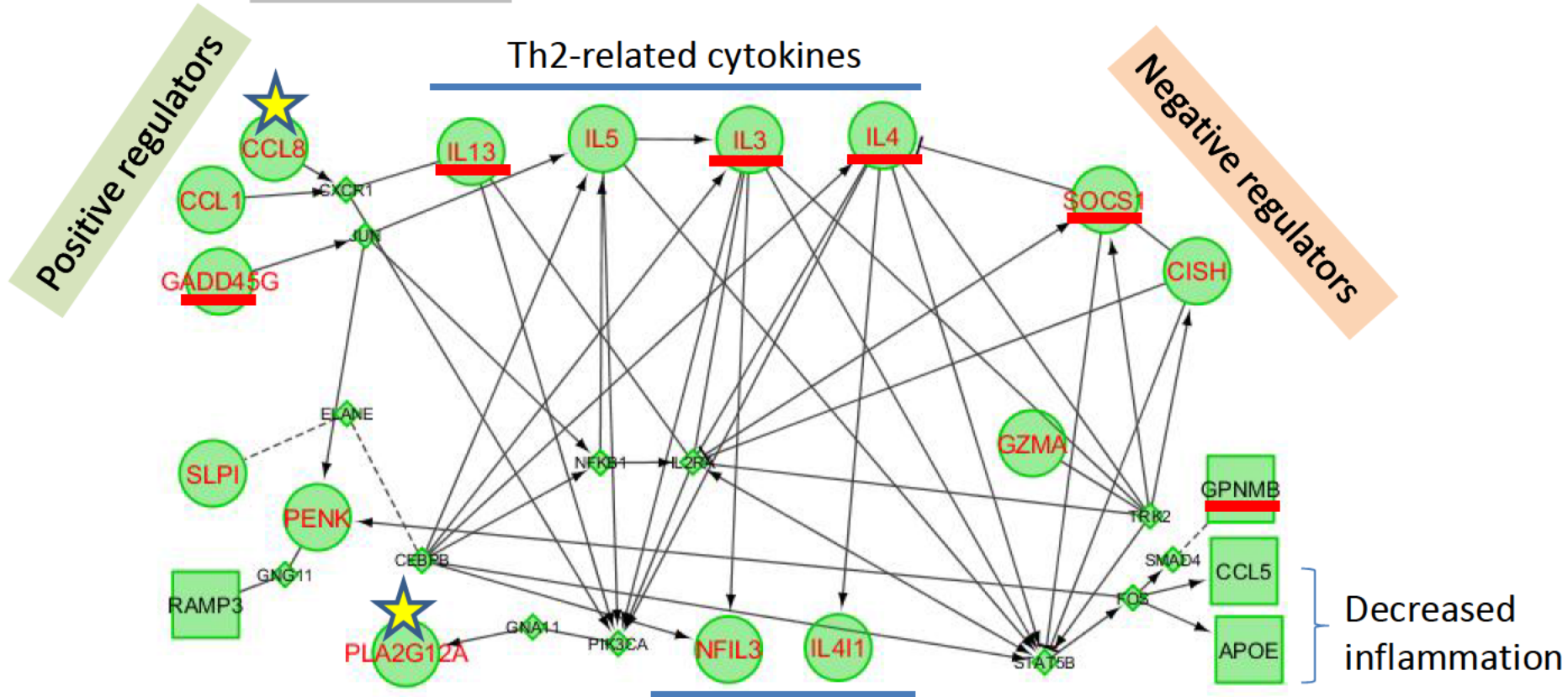


- Circles are up-regulated genes and squares are down-regulated genes
- Diamonds are "linking" gene

★ Present in RLD but just below arbitrary
 Reference ID: J0602248
 FC = 4.0 cut-off (FC = 3.7, 3.9)

Overlap Between Sandoz Study Data and Repeat of Teva Study

(b) (4)

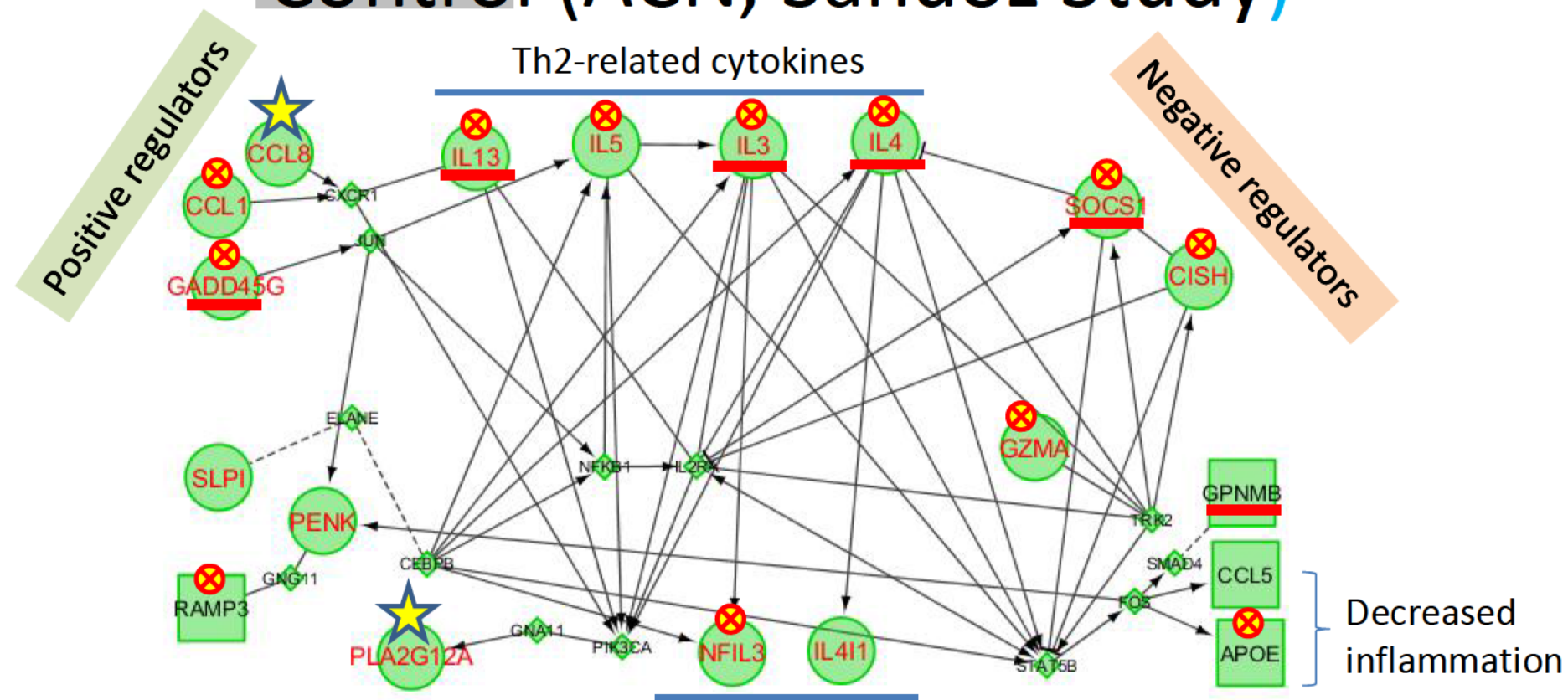


- Circles are up-regulated genes and squares are down-regulated genes
- Diamonds are "linking" gene

★ Present in RLD but just below arbitrary
 Reference ID: A692248
 FC = 3.7, 3.9

Downstream Th2 signals
 — DEGS in (b) (4) Sandoz Studies

Overlap with Chemically Inequivalent Control (ACN, Sandoz Study)



- Circles are up-regulated genes and squares are down-regulated genes
- Diamonds are "linking" gene

Downstream Th2 signals

— DEGS in (b) (4) Sandoz Studies
⊗ Genes altered by ACN control

★ Present in RLD but just below arbitrary
 Reference ID: 3602248
 FC = 4.0 cut-off (FC = 3.7, 3.9)

Summary: Pathway Analysis

- Biologically plausible pathways that appear to correlate with clinical effects can be constructed using gene expression data
- Sets of common genes can be identified:
 - Using different protocols (Teva vs. Sandoz studies)
 - Using drugs known to be chemically inequivalent (ACN vs. RLD)
- Conclusion: Gene expression data can suggest possible mechanisms that correlate with clinical effects, but remain inconclusive in determining therapeutic equivalence in the absence of other data, even with:
 - Adequate study design
 - Appropriate statistics
 - High levels of stringency in selecting DEGS

Summary & Conclusions

Consult No: 2014-0927

Question #1: Evaluate the data quality, sample variability (including method and batch to batch variability) and analytics and statistics used by TEVA on their gene expression studies related to comparing RLD Copaxone to generics.

Study design weaknesses, technical bias (both before and after statistical corrections), and inappropriate statistical analysis confound the published Teva studies and make them inconclusive.

Summary & Conclusions

Consult No: 2014-0927

Question #2: Are comparative data from these sorts of studies valuable to the assessment of sameness for generic Copaxones?

a) Are there any reliable differences between the RLD batches and generic samples in individual gene expression or pathways in the Teva studies?

No reliable differences in gene expression or pathways could be identified in the Teva (b) (4) or Sandoz studies.

b) Are any of the differences biologically plausible as relevant to product safety or efficacy?

N/A: No differences could be identified

c) If the answer to both (a) and (b) is yes, is there a feasible and robust experimental approach to test generic candidate products

N/A

Summary & Conclusions

Consult No: 2014-0927

Question #3: Please comment on the relevance and validity of using the gene expression experiment to correlate to the clinical effects of GA

Gene expression data alone are not considered a suitable approach to test generic candidate products, but may suggest possible mechanisms of actions only if the studies:

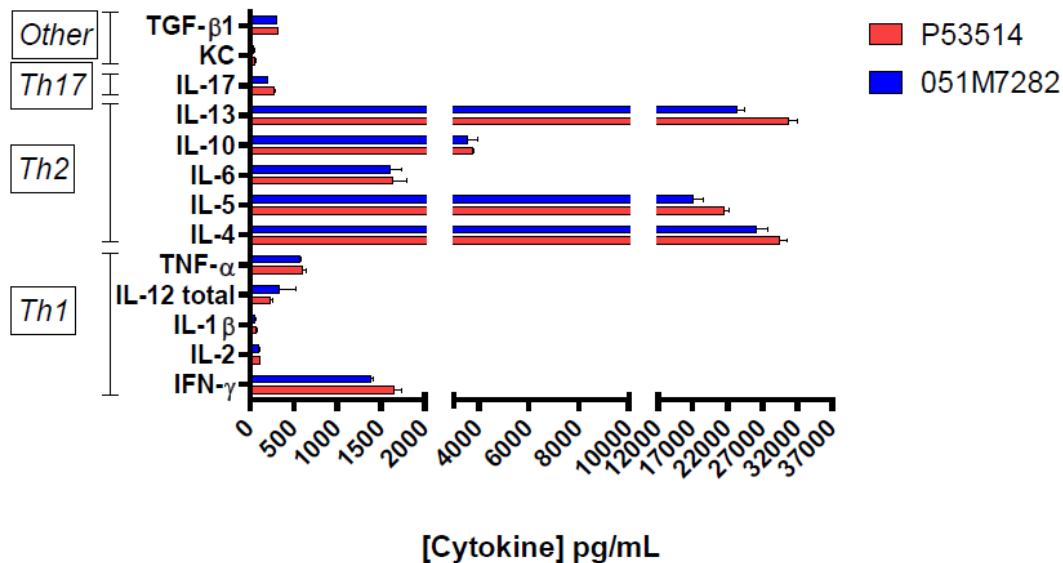
- (i) Are well controlled
- (ii) Are conducted in a therapeutically relevant model system
- (iii) Use appropriate analytics
- (iv) Are supplemented by confirmatory quantitative data from other assays, and
- (v) Consider the most informative pathway analysis approaches, e.g. some combination of algorithm-based pathway assignments and manual queries

BACK-UP SLIDES

Cytokine responses: RLD vs S/M

Glatiramer Acetate Injection, 20 mg/mL
3.2.S.3.1 Elucidation of Structure and other Characteristics

Sandoz Inc.
13 July 2012



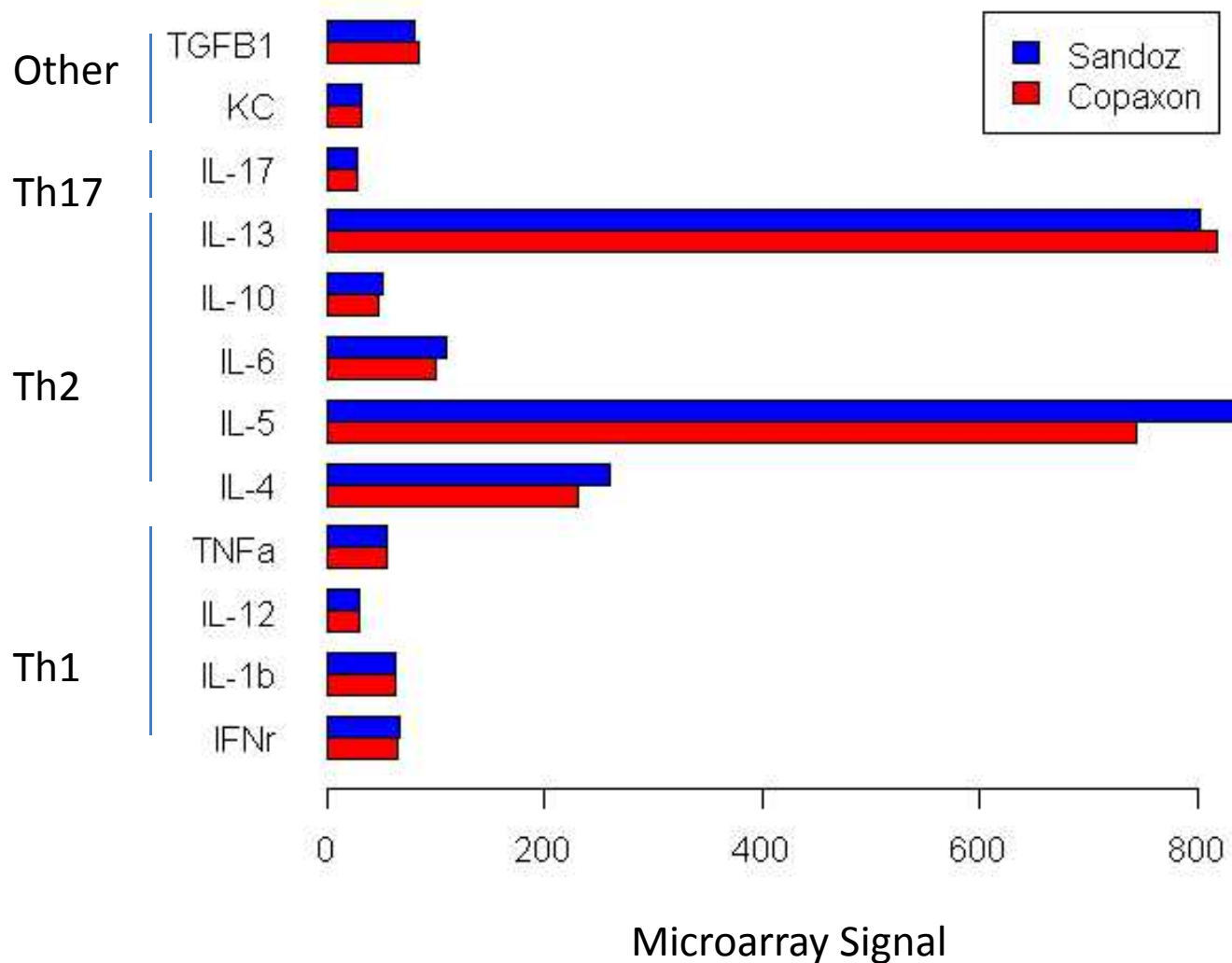
Data collected as part of assay development. S/M selected IL-4 as their index cytokine for potency method.

Blue = TEVA
Red = Sandoz/Momenta

Figure 45. Th2 Polarization Induced by Glatiramer Acetate

Antigen primed CD4+ T cells (1×10^6 /mL) were *ex vivo* stimulated with 20 µg/mL of RLD (Lot P53514) and the Glatiramer Acetate from a representative M356-Process-1.1.0 process validation run (Lot 051M7282), in the presence of T cell depleted mitomycin c treated naïve splenic APC (5×10^6 /mL). Cell-free conditioned media from the second round of stimulation was collected 45 hours post stimulation. Th1 (IFN-γ, IL-2, IL-1β, IL-12 total and TNF-α), Th2 (IL-4, IL-5, IL-6, IL-10 and IL-13), Th17 (IL-17) and other (KC and TGF-β1) cytokine levels (pg/mL) were measured using multiplex technology (MSD) and sandwich ELISA. The bar indicates the mean and the error bars are the SDs.

Cytokine *gene* responses: RLD vs S/M



Individual Patient Data

Human Gene Array Variability in Response to GA

Table 4b

Gene expression profiling in PBMC derived from MS patients before and after GA treatment

Genes altered	MS13	MS14	MS15	MS16	MS17	MS18	MS19
Fas	-	-	-	↑*	-	↓	↑*
NF-κB	-	↓	-	-	-	↓	-
iNos	-	-	↑	-	↑*	↑	↑
IP-10	↑	-	-	↑	-	-	-
1-8U	-	-	↑	↑	-	-	-
1-8D	-	-	↑	↑	-	-	-
ICAM-1	-	↓	↓	↓	↓	↓*	↓*
VLA-4	-	-	↓	↓	-	-	-
IL-15Ra	-	↓	↓	↓	↓	↓	-
IL-1b	-	↓	↓*	↓	↓	↓	↓
IL-8	-	↓*	↓*	↓	↓*	-	↓
CXCR4	↓*	↓	-	↓	-	-	↓*
ApoE	↓	↓*	-	↓	↓*	↓	-
CCR3	↑*	↑	-	-	-	-	-
IL-13	-	-	-	↓	-	↓	-
IL-12R B2	↑*	↑*	↑*	-	↑*	-	↑*
TGFβ1	-	-	-	↓	-	-	↑*
TNFα	-	↓	-	↓*	-	↓*	-
IL-12 p40	↑	-	↑	-	↑*	↑	-
No. of genes altered	6	10	10	14	8	10	8

Self-paired PBMC specimens were obtained in seven MS patients before and after GA treatment and analyzed by gene expression profiling. Data are expressed as changes in gene expression (post-treatment/pretreatment) by greater than 2 times or between 1.5 and 2 times (asterisks).

Individual patient responses in gene array data after 2 years of treatment with GA.

Differences between pretreatment vs. +2 years on treatment.

Similar variability seen with patients treated with β-IFN.

Reference: Hong et al
J. Neuroimmunol. **152** 126-139 (2004)

Individual Probe Signals for FOXP3

Probe ID	RS vs Medium	DP vs Medium	N vs Medium
ILMN_1225330	1.28*	1.24*	1.21*
ILMN_1251126	0.96	0.97	0.97
ILMN_2635132	1.40*	1.39*	1.28*
ILMN_2917180	1.37*	1.40*	1.33*

Table 1. Mean fold change of the microarray signals from the four FOXP3 probes between GA (including RS, DP) and medium, as well as GA-N and medium samples. Fold change values with an asterisk are statistically significant (FDR-adjusted p value < 0.05).

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/s/

SIMON S ENG
07/30/2014

Memo

Date: March 25, 2014

Revised April 3, 2014

Revised May 31, 2014

Revised June 5, 2014

Revised June 12, 2014

From: Fred Mills, Staff Scientist, DTP

To: Amy S. Rosenberg Director, DTP

Tracking numbers: ANDA 090218 (Sandoz/Momenta), ANDA (b) (4) (Mylan) (b) (4)
(b) (4)

Products: glatiramer acetate (GA) proposed generics for treatment of Multiple Sclerosis

Subject of Review: Biocharacterization for glatiramer acetate follow-on products

Recommendations

Glatiramer acetate (GA) for MS therapy is administered chronically and induces immune responses, a situation in which the Agency has always requested clinical data to support approval of biotherapeutics. However, generic products approved by the ANDA pathway do not require clinical studies. In the absence of clinical data for a complex mixture product whose mechanism of action is uncertain and for which it is likely that only a subset of the molecules mediate efficacy, the pathway for approval would rely on very stringent demonstrations of similarity from a great diversity of physicochemical and biological characterization assays. However, the unusual features of GA present difficulties for establishing biochemical equivalence.

Glatiramers are very complex, heterogeneous peptide mixtures for which, quite possibly, only a subset of GA molecules mediate either efficacy or safety effects. Because the product has such large number of different peptides and the functional contribution of each peptide to safety and efficacy is at present unknown, using chemical analyses to establish comparability between innovator and generic products may prove difficult or impossible. The concern is that glatiramer may have peptides with multiple potential modes of action whose relative contributions to clinical performance are not clear. Therefore, DTP considers that an optimal development pathway would involve demonstration of clinical comparability between the innovator product (Copaxone) and Sandoz/Momenta's or other generic products. However, a preponderance of evidence from both biochemical/biophysical analyses, plus functional studies, may potentially provide an acceptable basis to assert that patients would not be placed at increased risk of adverse clinical outcomes by treatment with generic glatiramer acetate. Specifically, DTP recommends that potential generic Sponsors provide data from the following set of comparative characterization studies (see below). It is critical that these studies be conducted using at least 10 lots of Copaxone and the proposed generic (ranging from newly manufactured and close to expiry). Selection criteria for the lots to be examined should be provided to the agency and the lots selected identified prior to testing

1. Gene Expression analysis

The innovator, TEVA, has published data which the company indicates are supportive of their view that the predictive value of physicochemical differences between Copaxone and certain potential generic products is poor. (Bakshi, S, et al. *Expert Opin Ther Targets*, 2013 17(4):351 - 362, Towfic, F., et al. *PLoS ONE*, 2014 9(1): e83757). In particular, these publications claim that the biochemical similarities between its innovator glatiramer Copaxone and the (b) (4) Natco biosimilar, failed to predict functional differences, as indicated by TEVA's gene expression arrays comparing RNAs expressed by cells treated with the two products. TEVA's analysis of these data suggest possible differences in multiple downstream pathways between Copaxone and proposed generics, However, independent analysis of TEVA's data by the FDA's OCP/DARS group indicates that TEVA's analysis is flawed, and that there may be no significant differences between the products.

Therefore, to provide a more robust assessment of glatiramer effects on gene expression, DTP recommends comparative profiling of RNA in at least 4 different human cell lines and primary human lymphocyte populations treated with Copaxone vs glatiramer acetate generic. The set of cells used should be relevant to MS, and should contain representatives of the CNS lineage, including cells of microglial phenotype. RNA-seq methodology, less error prone than other profiling methods, may provide the most complete and reproducible profiling. Additionally, RNA-seq profiling should capture microRNA expression, as there is literature indicating a role of microRNA in MS lesions (Thamilarasan et al. 2012, *Autoimmunity Reviews* 11, pp 174-179).

2. Physicochemical Characterization

New bioanalytical methodologies may be capable of detecting physicochemical differences between Copaxone and follow-on products. Therefore, DTP recommends that the Sponsor explore the use of technologies such as LC-MS-NMR and others to provide an in depth characterization of the products (reviewed in Berkowitz et al., *Nature Reviews Drug Discovery* 2012,11, pp. 527-540)

3. Long-term animal studies

The efficacy of GA therapy appears to involve several pathways including the generation of GA-specific regulatory T cells and an increase in GA-specific IgG4. In a Phase IV study (Karussis et al. *Journal of Neuroimmunology* 220 (2010) 125-130) designed specifically to assess immunogenicity, all GA-treated patients (153) developed GA reactive antibodies. While these antibodies did not show neutralizing activity, in long-term treated patients (ie>9 months) GA-reactive IgG4/IgG2 and IgG4/IgG1 ratios were inversely correlated with the annualized relapse rate (p=0.003) and the IgG4 levels to the number of relapses (p=0.0037). Similar results were seen in an earlier, smaller study, in which antibodies of the IgG1 subclass predominated early in therapy, peaked at 9 months, and were followed by an increase in IgG4 (Basile et al. *Journal of*

Neuroimmunology 177 (2006) 161–166). This isotype progression is consistent with a likely mechanism of action: development of a GA-specific T-helper 2 (Th2) T-cell response, thus deviating the immune response from a destructive Th1 response. Indeed there are data indicating that both T and B cell responses may mediate the activity of the product (for review, see Lalive et al., 2011, CNS Drugs 25, pp. 401-414)

Therefore, in addition to the MS animal models already agreed to between FDA and sponsor, it would be ideal to examine comparability in functional studies using long-term animal MS models, such as the TMEV mouse viral model, or marmoset EAE. These studies should include measurement of GA-specific antibody isotype distribution. The model(s) should involve repeated treatment of ongoing CNS disease, rather than models where the product is administered prophylactically. Any studies involving animals should avoid the use of adjuvants that promote Th2 responses, since such adjuvants can hinder the interpretation of the results.

Table of Contents

Section	page
Heading	1
Recommendations	1
Table of contents	4
Executive Summary	6
Copaxone Background and Literature	12
Listing of Galtiramer Acetate follow-on products	14
Excerpts from TEVA briefing package for the March, 2014 meeting with the FDA	15
Physicochemical analysis of differences	16
Mouse Splenocyte model	19
cDNA array results	19
Genes differentially expressed by Copaxone vs. Natco follow-on Show four general patterns	20
Variability of Natco	20
Human THP-1 monocyte cell line studies	21
Significant upregulation of genes in inflammatory pathways for Natco vs. Copaxone.	21
Probioglat Clinical Experience in Mexico (provided in the TEVA slide presentation)	22
Protiramer Experience (from literature and TEVA briefing)	23
ANDA 90218 Biocharacterization data for Sandoz/Momenta GA product	25
Release Methods	
Secretion of IL-4 by mouse Th2 cells in response to GA stimulation	26
Western Blot with polyclonal antibody	26
Identity test with Mab panel	27

Primary characterization Methods	27
THP-1 Chemokine assay	27
Generation of Murine Th2 Polarized T Cells	28
Anti-Glatiramer Acetate Antibody Response	29
EAE models	31
MOG 35-55 active immunization /prophylactic dosing study	31
Adoptive Transfer Model	34

	(b) (4)	37
		37
		38
		38
		38
		41
		42
		43
		46
		49
		49
		50
		51
		52
	54	

Executive Summary

Glatiramer acetate is a mixture of synthetic peptide copolymers of 5000-9000 dalton size containing alanine, glutamic acid, tyrosine, and lysine, with these amino acids present in average molar fractions of 0.427, 0.141, 0.095, and 0.338, respectively. TEVA's innovator product, Copaxone, is licensed for treatment of MS, with (b) (4) follow-on products in development.

There is considerable literature on immunogenicity of the innovator product, which was licensed in 1996. Copaxone is a mix of foreign peptides, and is highly immunogenic, with all patients eventually raising antibodies (Varkony et al., Expert Opin. Pharmacother. (2009) 10(4) 657-668). Antibodies of the IgG1 subclass predominate early in therapy, peaking at 9 months, followed by an increase in IgG4 (Basile et al. Journal of Neuroimmunology 177 (2006) 161-166). This is consistent with development of a GA-specific T-helper 2 (Th2)-like T-cell response, which may be one mechanism of action. Increased IgG4/IgG1 and IgG4/IgG2 ratios correlate with a reduced rate of MS relapse.

This review contains discussion of biological characterization data provided by Sponsors for (b) (4) proposed generic products: Glatiramer Acetate (ANDA 090218, Sandoz/Momenta), GMA (b) (4) Mylan Pharmaceuticals (b) (4) (b) (4). The physicochemical characterization of these products is being reviewed by the Office of Generic Drugs, which has requested this consult.

As important background, data from the briefing document supplied by TEVA for the February 24, 2014 meeting with the FDA are also discussed. Much of these data are also published (Bakshi, S, et al. Expert Opin Ther Targets, 2013 17(4):351- 362, Towfic, F., et al. PLoS ONE, 2014 9(1): e83757). Using Capillary Isoelectric Focusing, particle size distribution analysis, and ion mobility mass spectrometry, TEVA has found significant physicochemical differences between Copaxone and three follow-ons, two of which are licensed outside the USA: Natco (b) (4), Escadra (marketed in Argentina), and Probioglat (licensed in Mexico).

TEVA's biological comparisons consist of cDNA array expression data from mice treated in vivo with Copaxone or a proposed generic, with splenocytes from these mice then stimulated in vitro with glatiramer products. Data are also provided from in vitro stimulation of the human THP-1 monocyte cell line with glatiramers. In the mouse splenocyte studies, TEVA found that Copaxone significantly impacts > 1,400 genes, and > 100 pathways. Comparing multiple Copaxone lots with multiple Natco lots revealed that: (1) 75 genes were differentially regulated between Copaxone and Natco (2) Natco-treated splenocytes showed considerably greater variability in gene response than Copaxone. Notably, FoxP3, a marker for Treg cells-which would help to dampen the inflammatory processes in MS, is more strongly upregulated by Copaxone, and with less variability in response compared to Natco. Moreover, more FoxP3 targets are upregulated by Copaxone. Using the THP-1 human monocyte data, TEVA found that relative to Copaxone, Probioglat upregulated CD14, a potential contributor to

inflammation, as well as a number of other inflammatory response pathway genes. Probioglat also upregulated MMP9 (Matrix Metallo Protease 9), which can facilitate T cell migration into the CNS. Similar observations were seen for Protiramer, which is TEVA's high molecular weight glatiramer that was withdrawn from clinical trials due to serious adverse events seen in rat and monkey preclinical models. These SAEs included injection site reactions, behavioral changes, weight loss, and deaths in both the rat and monkey studies that were attributed to Protiramer.

Sandoz/Momenta has provided biological characterization data for ANDA 090218.

These data are extensive (although lacking the genome-wide power of the TEVA data). The studies include IL-4 secretion in Th2 cells prepared from mice treated with Copaxone or the Sandoz glatiramer, then stimulated with these glatiramers in vitro. The curves for secretion of IL-4 vs. glatiramer concentration follow each other closely for Copaxone and the Sandoz product. The Th2 phenotype of similarly treated T cells was assessed via cytokine profiling for IL-4, 6, 10, 13 (Th2), IFN- γ , IL-2, IL-1- β , IL-12, TNF- α (Th1), IL-17 (Th17), and TGF- β 1 and KC (Keratinocyte-derived Chemokine), which are associated with other T cell phenotypes. The profiles were strongly Th2, and indistinguishable for Copaxone vs Sandoz GA. Similarly, the THP-1 monocyte cell line was stimulated with glatiramers + IFN- γ , and found to give very similar MIG chemokine secretion curves for Copaxone vs. Sandoz GA.

The isotype distributions of anti-GA antibodies from mice treated up to 28 days with Copaxone or Sandoz GA were similar. The most highly expressed isotype after 28 days was IgG1, which is the mouse isotype (together with IgE) that is stimulated by Th2 cells. Thus these data are consistent with an expected GA induction of a Th2 response, and by this criterion, there was no difference between Copaxone and Sandoz GA. A human IgG4 response can be taken as a "readout" for Th2-based efficacy. However, the transition to this human Th2 isotype is seen after long term dosing (9 months) and this aspect of treatment has not been replicated by the mouse antibody model, because this was a short term (28 day) study.

Sandoz/Momenta, as per agreement with the FDA, in a May 24, 2012 teleconference, provided data from three EAE models; i.e.

a) Prophylactic dosing using active immunization with Proteolipid Peptide (PLP₁₃₉₋₁₅₁) in the SJL/J strain of mice

Relapsing -remitting model, 25-40 day duration (if extended in 2nd relapse peak)

b) Prophylactic dosing using active immunization with Myelin Oligodendrocyte Glycopeptide (MOG₃₅₋₅₅) in the C57Blk/6 strain of mice

Chronic progressive model

c) Therapeutic dosing using the adoptive transfer model with Proteolipid Peptide (PLP₁₃₉₋₁₅₁) in the SJL/J strain of mice.

This model is used to study the effector state of EAE, independently of the immunization phase.

Overall, I agree with the Sponsor that the EAE results do not show a difference between Copaxone and the Sandoz/Momenta product. The importance of EAE models for MS is seen from the fact that the major MS biologics (IFN- β , GA, and anti-VLA-4 antibody) have shown a correlation between model EAE results and therapeutic efficacy. Although EAE mice treated with glatiramer, show Th2 polarization,, there are many examples of EAE treatment successes that have not translated into similar MS success, including IFN- γ , and Myelin-Basic Protein oral tolerance. Perhaps most significant for assessing similarity between GA products is the inability of the EAE models to mirror the long-term beneficial immunological modulation that is an important aspect of Copaxone therapy for MS. Therefore, I find that the while similar results for Copaxone and Sandoz GA seen in EAE may provide necessary support for comparability, by themselves they are not sufficient to provide assurance that the two products will have similar safety and efficacy profiles in the treatment of human MS

I also have an unresolved concern regarding deficiencies from the OGD CMC review that may impact safety and efficacy. Deficiency 19 (p.191 of the CMC review) requested that the Sponsor provide assurance that aggregation was assessed near the expiration of validated storage time. Furthermore, OGD requested that the Sponsor perform a one-time study with the orthogonal method they have developed to assess aggregation under long-term and accelerated storage conditions. Because aggregation has the potential to alter immune responses, I have asked OGD to clarify the status of this deficiency.

(b) (4)



Following this page, 2 pages withheld in full - (b)(4)

General Comments on Biocharacterization of potential glatiramer acetate follow-on products for MS

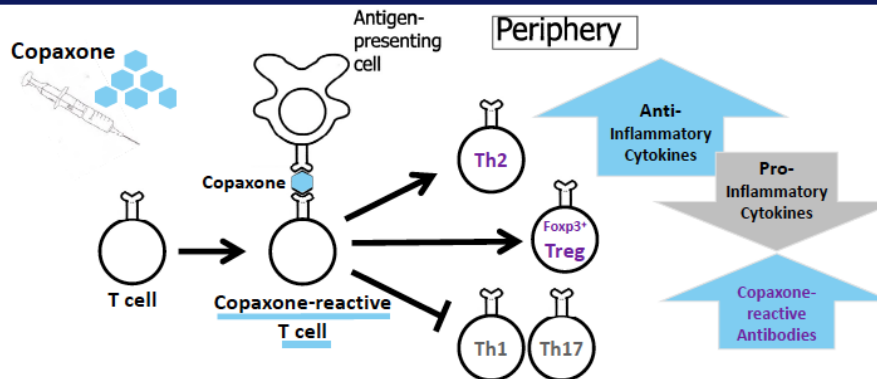
The data provided, especially for the Sandoz/Momenta product, is quite extensive, and is consistent with biological characterization studies for a well-defined biologic derived by recombinant DNA technology, such as a monoclonal antibody, cytokine, or enzyme replacement product. However, glatiramers are very complex peptide mixtures, the species mediating efficacy are not understood, and there are multiple potential modes of action whose relative contributions are not clear. Thus analytical characterization and use of appropriate animal models of MS, would seem necessary, but not sufficient to establish comparability between Copaxone and follow-ons. Similar thinking could apply to the elegant array data provided by TEVA; i.e. while indicating differences in multiple pathways between Copaxone and follow-ons, the impact of these differences on MS treatment efficacy and safety is not known, and establishing actual cause and effect would involve major research studies that would have clinical components. Furthermore, the long-term potentially beneficial immunologic correlates of glatiramer therapy (such as GA-reactive IgG4) may not be easily replicated in animal models.

Copaxone Background and Literature

Glatiramer acetate is a mixture of synthetic peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate synthesis reaction are L-alanine (Ala, A), L-glutamic acid (Glu, E), L-tyrosine (Tyr, Y), and L-lysine (Lys, K). The drug product contains these amino acids with an average molar fraction of 0.427, 0.141, 0.095, and 0.338 respectively. The purified drug product has an average molecular weight of 5000-9000 Da. Copaxone is the innovator product, for treatment of MS, and there are at least ^(b)₍₄₎ potential generics for this indication in various stages of development.

There is considerable literature on immunogenicity of the innovator product, which was licensed in 1996. Copaxone is a mix of synthetic peptides that do not necessarily replicate native sequences, and is highly immunogenic, with all patients eventually raising antibodies (Varkony et al., *Expert Opin. Pharmacother.* (2009) **10**(4) 657-668). Antibodies of the IgG1 subclass predominate early in therapy, peaking at 9 months, followed by an increase in IgG4 (Basile et al. *Journal of Neuroimmunology* 177 (2006) 161-166). This is consistent with development of a GA-specific T-helper 2 (Th2)-like T-cell response, which may be one mechanism of therapeutic action.

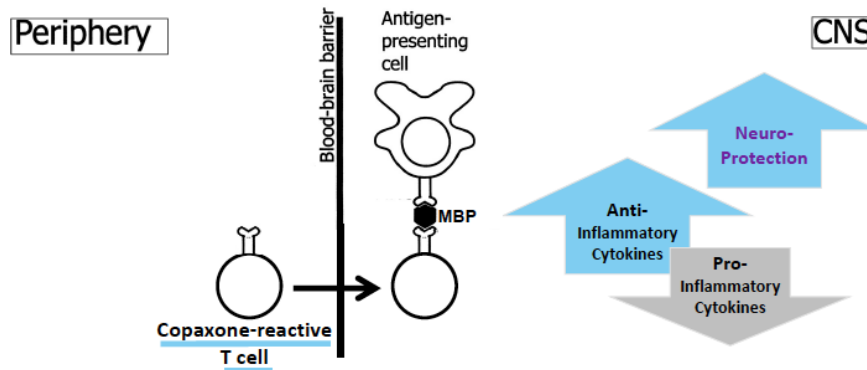
Antigenicity of Copaxone is Critical to its Function



- ❑ Copaxone is an antigen that binds to antigen presenting cells (APCs), inducing a specific shift from pro-inflammatory (Th1/Th17) to anti-inflammatory Th2, regulatory T (Foxp3⁺ Treg), and B cells
- ❑ Copaxone also induces non-neutralizing, Copaxone-reactive specific antibodies that are associated with clinical response**

TCR = T-cell receptor. Treg = regulatory T cell. Th = T helper cell. Foxp3 = Forkhead box P3 transcription factor.
Figure modified based on Hohlfeld, & Wekerle, *PNAS* (2004). *Farina et al, *J Neuroimmunol* (2002); Brenner et al, *J Neuroimmunol* (2001)

Current Understanding of MoA in the CNS



- ❑ Copaxone-reactive Th2 and Foxp3+ Treg cells migrate into the CNS and cross react with Myelin Basic Protein (MBP) and other autoantigens, inducing secretion of anti-inflammatory cytokines
- ❑ Copaxone induces secretion of neurotrophic factors (e.g. BDNF, NT-3, NT-4)

Figure modified based on Hohlfeld & Wekerle, PNAS (2004)

There is also documentation of anaphylaxis in 66 out of approximately 80,000 treated patients (Rauschka et al. *Neurology* 2005;64:1481-1482, Gomis et al. *J Investig Allergol Clin Immunol* 2012; Vol. 22(1): 63-79). A hypothesis has been advanced that the Th2 response induced by Copaxone may predispose some patients to IgE reactions. As a caveat, approximate 10% of patients develop an immediate post-injection systemic reaction (IPISR) that may mask diagnosis of true anaphylaxis.

Finally, a retrospective phase IV study was conducted to evaluate the anti-GA antibody subtypes, test their in vitro neutralizing activity by assessing the ability of patient sera to inhibit the proliferation of a glatiramer-specific cell line stimulate with GA, and correlate these parameters with clinical efficacy, in long-term GA treatment of MS patients (Karussis et al. *Journal of Neuroimmunology* 220 (2010) 125–130). Serum samples were analyzed from 153 MS patients, 126 treated with GA for 2 to 15 years (mean 6.6 years) and 27 treated for <2 years. This study did not demonstrate neutralizing activity, as assessed by inhibition of GA-stimulated cells by patient sera. However, ratios of GA-reactive IgG4/IgG2 and IgG4/IgG1 ratios were inversely correlated with the annualized relapse rate long-term treated patients ($p=0.003$) and the IgG4 levels to the number of relapses ($p=0.0037$), but only in long-term treated patients.

Reviewer comments

It should be noted that these observations of correlation between IgG subtype ratios and relapse rate are phenomenological without a identified mechanism. Increased IgG4 ratios are might simply be a readout for increased, beneficial Th2 activity, by deviating the immune response away from destructive Th1 responses. Alternatively, the antibodies themselves could mediate a beneficial effect, such as shielding of axons by an antibody that does not fix complement (IgG4) and thus blocks binding by antibodies that do fix

complement (IgG2)

Potential Follow-On Galtiramer Acetate Products

Glatiramer Acetate Sandoz/Momenta

Probioglat Farmatel (Mexico)



Escadra Marketed by Raffo in Argentina

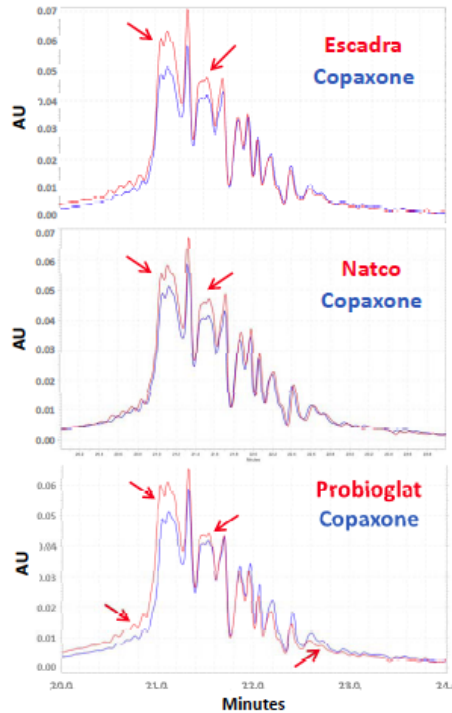
HangZhou China (sold as an API)

TEVA briefing document for March 25, 2014 meeting with FDA

Physicochemical analysis of differences

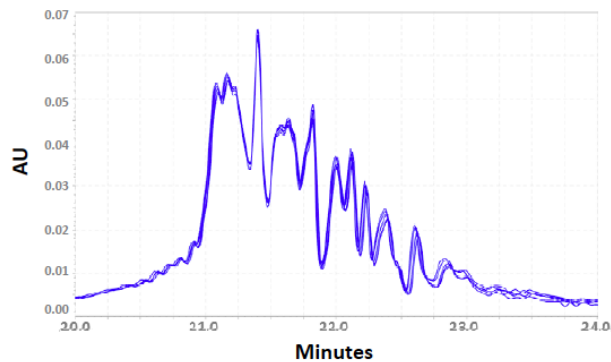
Charge Distribution of Purported Generics

- Distribution pattern from capillary electrophoresis (CE) is different for each glatiramoid, demonstrated by Copaxone overlaid on Natco, Escadra and Probioglat
- Differences in charge distribution (composition) are highlighted by red arrows



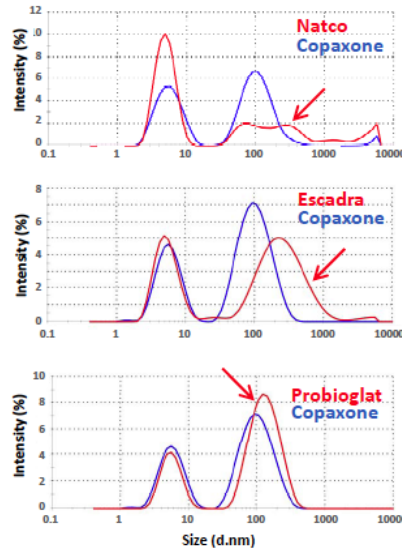
In their briefing document, TEVA provide a figure showing a tight CE distribution of CE peaks for 5 Copaxone lots, indicating good reproducibility. The number of Escadra, Natco, and Probioglat lots analyzed was not provided, so one cannot assess their reproducibility for this property.

Charge distribution pattern of 5 randomly chosen Copaxone batches shows tight consistency based on capillary electrophoresis (CE)



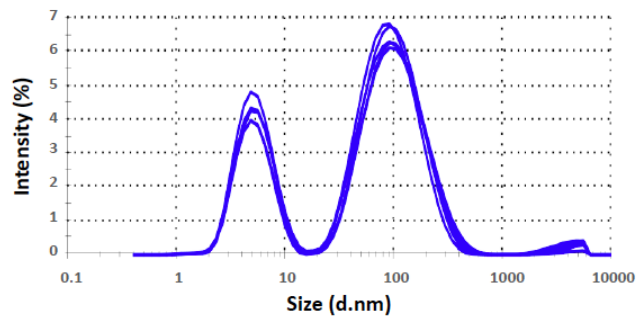
Particle Size Distribution of Purported Generics

- Difference in aggregate size in colloidal solutions of Copaxone and purported generics as detected by DLS



In their briefing document, TEVA provided a figure showing a tight DLS distribution of CE peaks for 5 Copaxone lots, indicating good reproducibility, again, as per the CE data, the number of Escadra, Natco, and Probioglat lots analyzed was not provided, so one cannot assess their reproducibility for this property.

Analysis of **10** randomly chosen Copaxone batches shows minimal size differences by Dynamic Light Scattering (DLS)



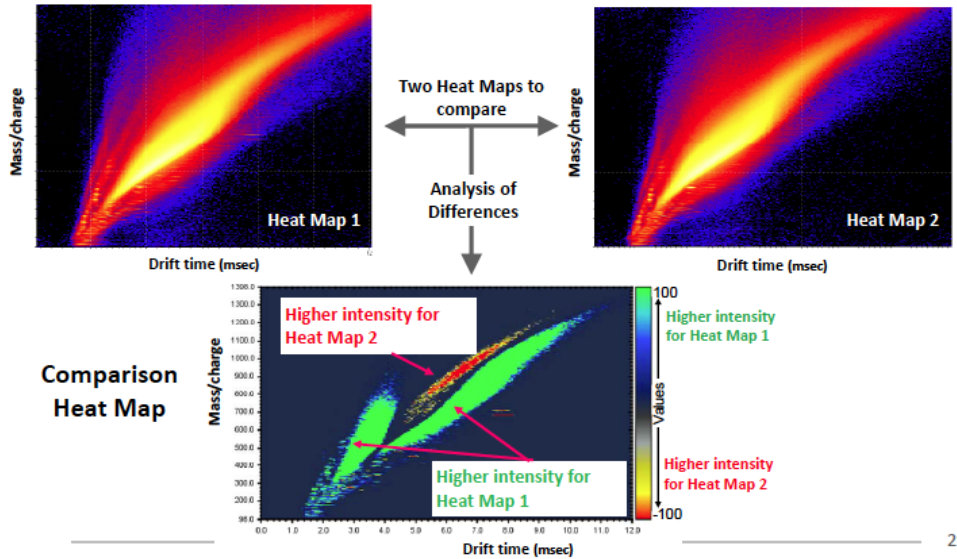
Ion Mobility Mass Spectrometry

See Berkowitz et al., Nature Reviews Drug Discovery 2012,11, pp. 527-540 for general background

HDMS Compare Software evaluates each pixel from two Heat Maps and calculates differences

Comparing Heat Maps to Identify Differences

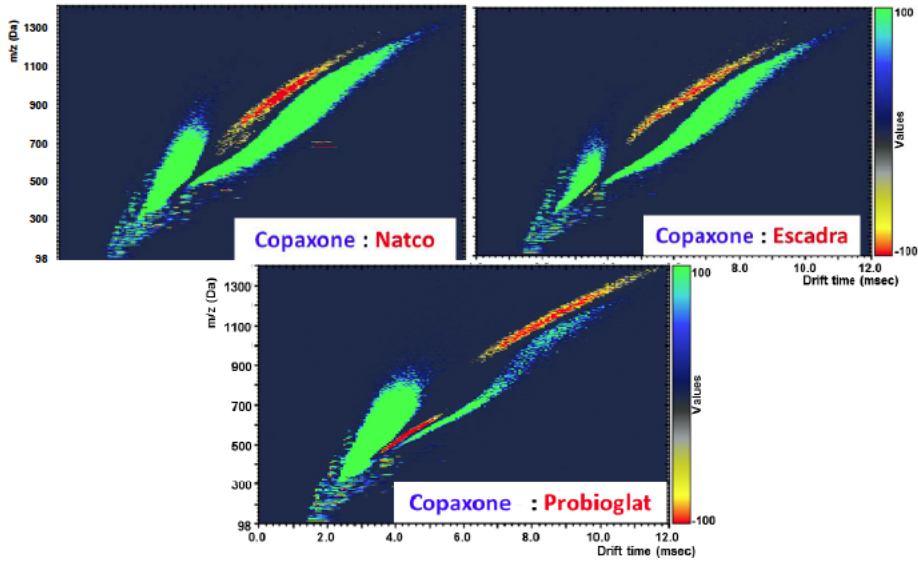
The *HDMS Compare Software* evaluates each pixel from two Heat Maps and calculates differences



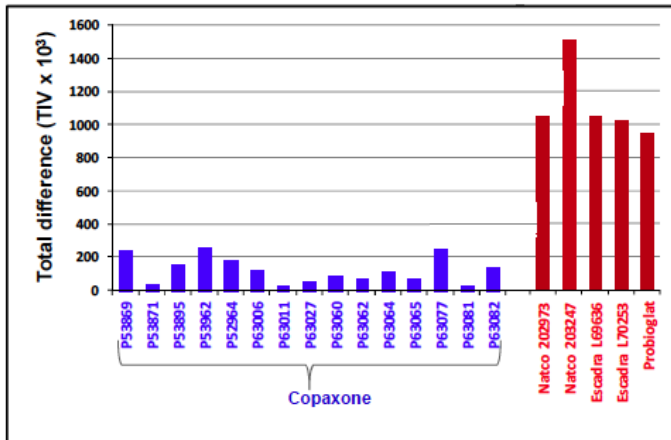
The studies shown in these figures assess gene expression from splenocyte cDNA (prepared, and analyzed by hybridization to an ^{(b) (4)} microarray, which measures ^{(b) (4)} transcripts) from mice which are injected for 3 days with glatiramer, the spleens then harvested, prepared and cultured with Copaxone, follow-on products, or controls per the method in Bakshi, S, et al. Expert Opin Ther Targets, 17(4):351-362 (2013) Towfic, F., et al. PLoS ONE, 9(1): e83757 (2014)

Profound Differences Copaxone vs. Purported Generics

Copaxone (P-53961) versus 3 Generics - (4 injections each)

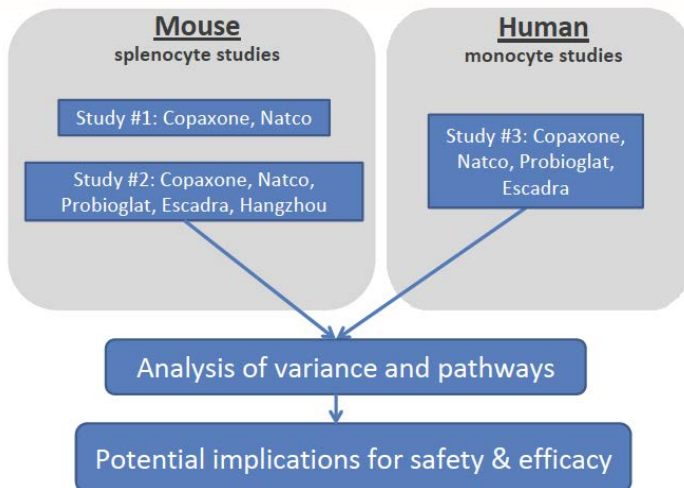


Total Intensity Value Comparison



Reviewer comment

With this methodology, 13 Copaxone lots appear to show limited variability among themselves, relative to their differences from 5 Natco lots.



Mouse Splenocyte model

Mice are injected for 3 days with glatiramer, splenocytes are then prepared and cultured with Copaxone, follow-on products, or controls

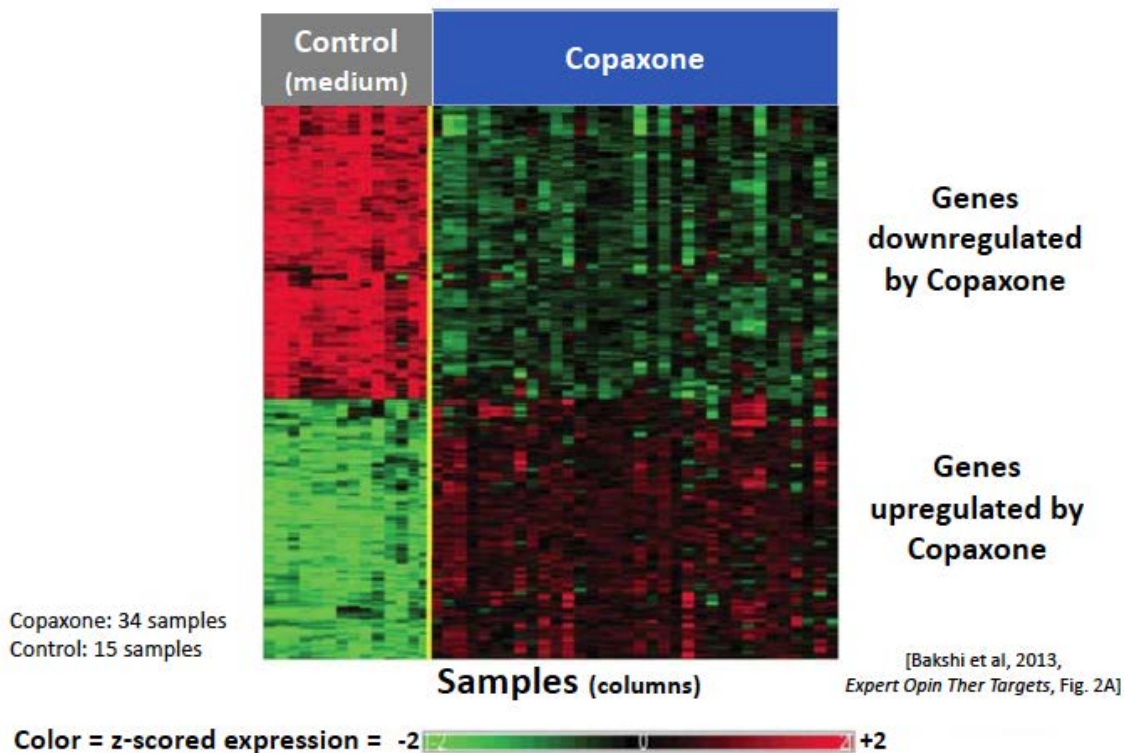
Bakshi, S, et al. Expert Opin Ther Targets, 17(4):351- 362 (2013)

Towfic, F., et al. PLoS ONE, 9(1): e83757 (2014)

After culture, splenocyte cDNA is prepared, and analyzed by hybridization to an (b) (4) (b) (4) microarray, which measures (b) (4) transcripts

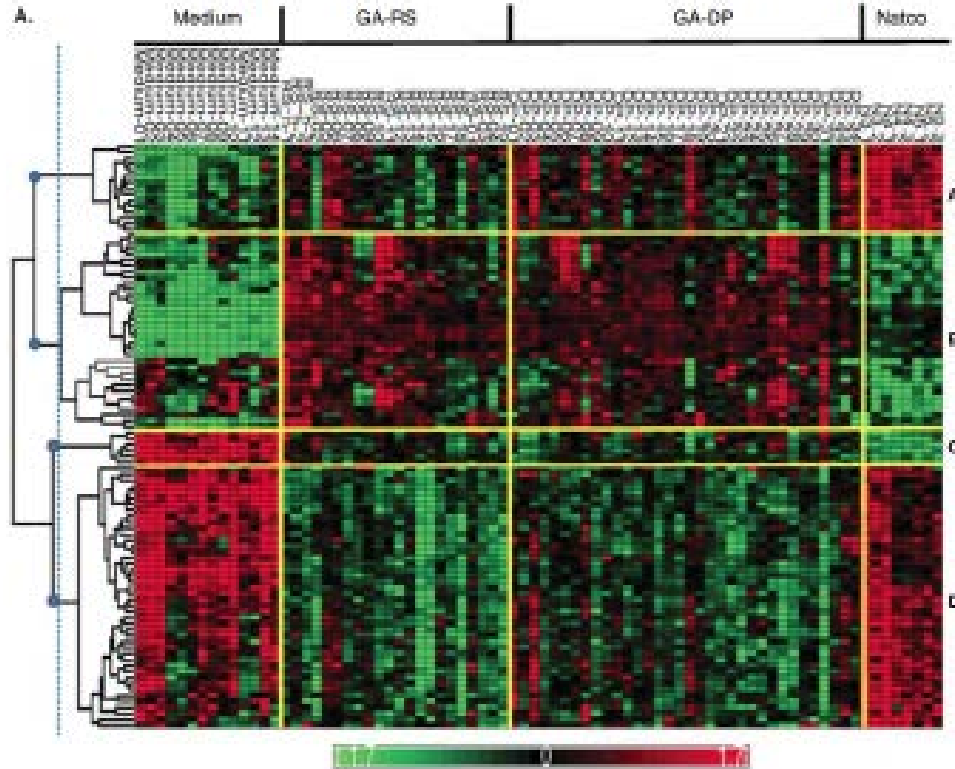
cDNA array results

Copaxone significantly impacts > 1,400 genes, > 100 pathways



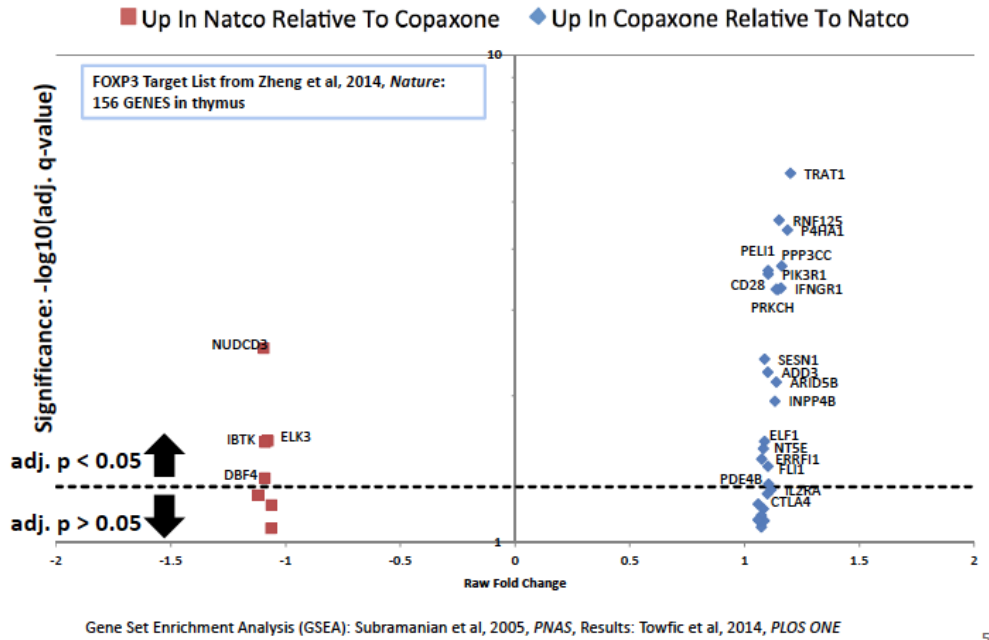
75 genes differentially expressed

Figure 3: Genes differentially expressed by Copaxone (GA-RS and GA-DP) versus a proposed generic (Natco) follow four general patterns



Variability of Natco

Copaxone upregulates FoxP3 more strongly than Natco, with a less variability (4.2x) in response. Copaxone also upregulates FoxP3 targets more than Natco, as seen in the following figure.



Natco also differentially upregulates GPR83

Human THP-1 monocyte cell line studies

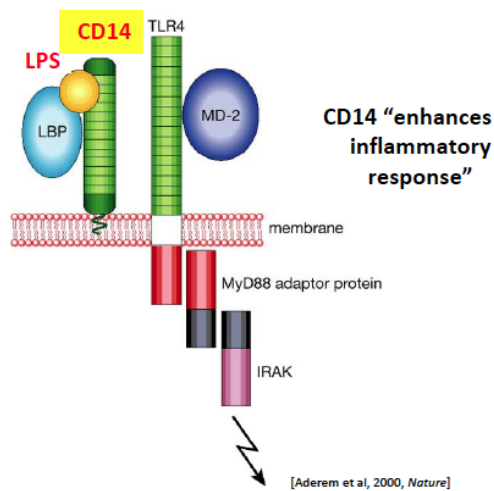
THP-1 human monocytes (TIB-202) were maintained in culture. Prior to treatment cells were passed and plated in a 6-well plate at a concentration of 1.0×10^6 cells/mL. Cells were allowed to recover for four hours after passage (prior to treatment). Using a predetermined non toxic concentration, the cells were spiked with $50 \mu\text{g/mL}$ of either Copaxone, GA/RS, Escadra, Probioglat, or Natco. $100 \mu\text{g/mL}$ mannitol was spiked as a negative control (vehicle). Each sample was analyzed in six replicates. In the mouse splenocyte model, CD14 was found to be upregulated. This was confirmed in the THP-1 model.

“CD14 is expressed in abundance on the surface of mature monocytes and in trace amounts on granulocytes, but not on other hematopoietic cells”

[Simmons et al, 1989, Blood]

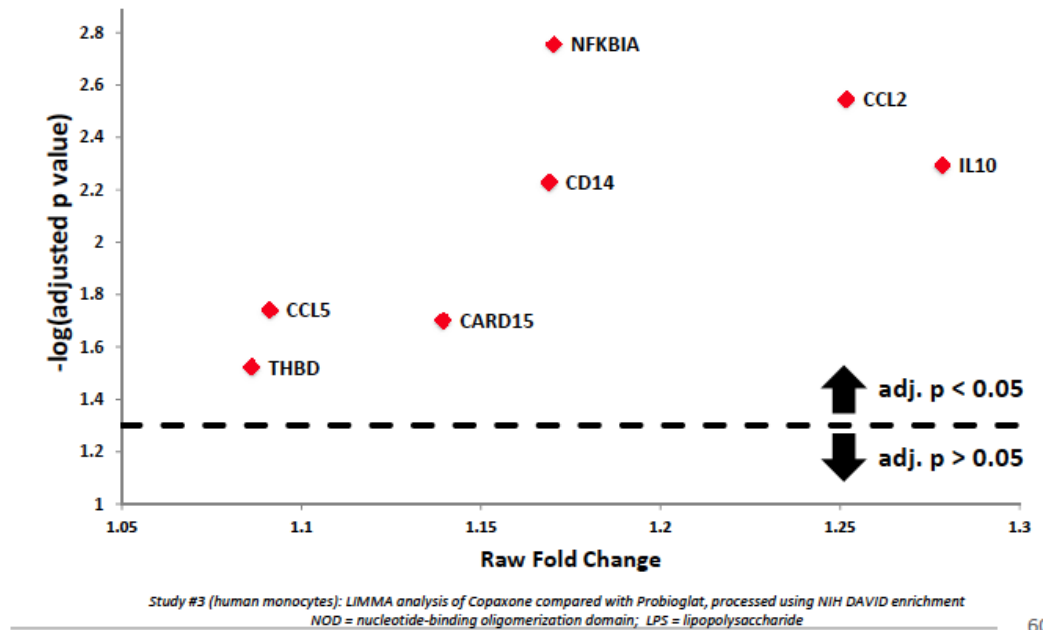
Monocytes may serve as “prominent contributors” to neuroinflammation in multiple sclerosis

[Bar-Or et al, 2003, Brain]



In the THP-1 model, Probioglat (licensed in Mexico by Farmatel) upregulates CD14 significantly more than Copaxone (well as TLR 2 and CD40) Moreover, in this model, Probioglate up-regulates pro-inflammatory response pathways, as seen in the following figure.

Significant enrichment for this pro-inflammatory response pathway among genes upregulated by Probioglat: adj. p = 2.86×10^{-3}



Probioglat induces significantly higher expression of *MMP9* than does Copaxone (Adj. p = 2.07×10^{-5} by LIMMA for Copaxone vs. Probioglat at 6 hrs in human monocytes). *MMP9* is an established biomarker and potential predictor of disease activity in MS. This finding is particularly concerning given the fact that *MMP9* facilitates T-cell migration into the CNS, playing a key role in the disruption of the blood–brain barrier (BBB) and thus in the pathogenesis of MS

Probioglat Clinical Experience in Mexico (provided in the TEVA slide presentation)

Probioglat was launched in Mexico January 2013. Hospital la Raza (Mexico City) follows 232 MS patients regularly. This is one of the three biggest hospitals of the IMSS (Instituto Mexicano de Seguro Social), and 65 patients have been treated with both Probioglat and Copaxone since January 2013. There has been an increase in injection site reactions, painful local reactions, erythema and diffuse flush, pruritus and chest pain. Greater than 50% of the patients experienced a relapse within 2-4months of switching, and relapse related hospitalizations increased 200% in 2013

Reviewer comment

I have at present been unable to find publications to substantiate these claims regarding Probioglat adverse events. Only reports in the Mexican media were found to corroborate the claim (<https://www.youtube.com/watch?v=AjFWvubhSFQ>)

Protiramer Experience (from literature and TEVA briefing)

Caution in consideration of glatiramer follow-on products is also indicated by TEVA's experience with protiramer (TV-5010- Varkony et al., *Expert Opin. Pharmacother.* (2009) **10**(4) 657-668). Hypothetically, higher molecular weight polypeptides could contain a greater number or variety of epitopic sequences with which to stimulate APCs and T cells. Protiramer is a higher MW glatiramoid that contains the same amino acids as GA in the same molar ratios and is prepared by making small adjustments to reaction conditions used in GA synthesis. The average MM of protiramer ranges from 13,500 -- 18,500 daltons .

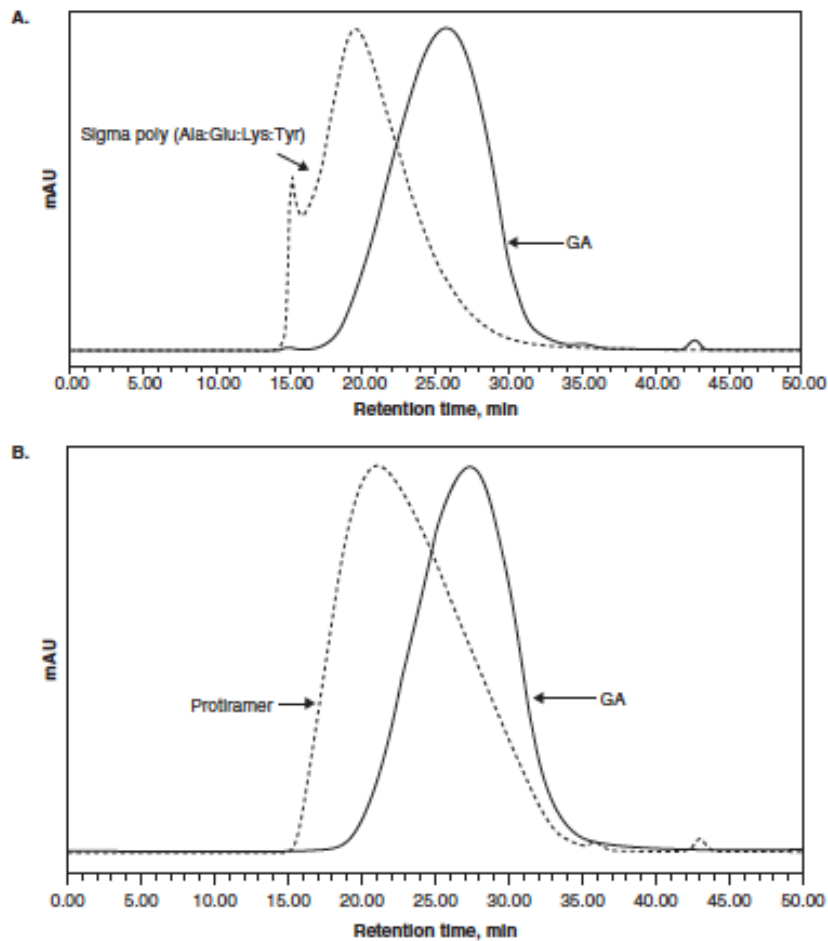


Figure 5. Molecular mass distribution of A. GA and Sigma Poly(Ala:Glu:Lys:Tyr) and B. GA and protiramer.
Reproduced from [15] © Informa Healthcare.
GA: Glatiramer acetate.

B ased on
generally favorable safety results from short-term toxicity studies, protiramer was approved for testing in two small multi-center, open-label, 9-month Phase II clinical trials in RRMS patients. Although 30 mg/week protiramer significantly reduced the number of Gd-enhancing and new T2-weighted lesions, similar reductions in these MRI measures during the pretreatment phase confound these findings. Based on results of long-term animal toxicity studies, protiramer development was halted. The serious toxic effects of protiramer were not apparent during short-term (3-month) toxicity studies, which were

completed with no serious AEs detected. Severe toxicity only became apparent after ~ 9 months of protiramer dosing. In the mouse splenocyte model, the gene with elevated expression for TW-5010 relative to Copaxone, that was most significant was MMP14 (Matrix Metallo-Protease 14). The observed upregulation of *MMP14* was striking because *MMP14* has been associated with fibrosis and eosinophil-related disorders in the literature, the very same toxicities seen in animals following long-term treatment with TV-5010. In addition to *MMP14*, another gene, (STAT3), which has also been linked to fibrosis, also showed significantly elevated expression in response to TV-5010 relative to Copaxone.

ANDA 090218 **Glatiramer Acetate (Sandoz/Momenta)**

From the Sponsor's Sept. 26, 2012 submission

Release Methods

Secretion of IL-4 by mouse Th2 cells in response to GA stimulation

This *in vivo/ex vivo* protocol which involves the following steps:

- 1) Injection of Balb/c mice with RLD and Complete Freund's Adjuvant (CFA) on Day 1;
- 2) Isolation of CD4+ T cells from the draining inguinal lymph nodes (LN), which are harvested on Day 11.
- 3) Successive rounds of *ex vivo* Glatiramer Acetate re-stimulation of these CD4+ cells through APC presentation, and then culture in the presence of IL-2 for bulk expansion and creation of a cell bank.
- 4) Measurement of IL-4 release by ELISA

These Th2 polarized T cells are characterized by their cytokine secretion profile in response to Glatiramer Acetate ; i.e. production of high levels of the anti-inflammatory Th2 cytokines IL-4, IL-5, IL-6, IL-10 and IL-13 and low levels of the inflammatory Th1 cytokines IL-2, IL-12p70, TNF- α , IFN- γ , and the Th17 cytokine IL-17. The release of the Th2 specific cytokine IL-4 from these bulk expanded cells is used as a read out of antigen specific T cell function for comparative studies of the test sample with Reference Licensed Drug (RLD).

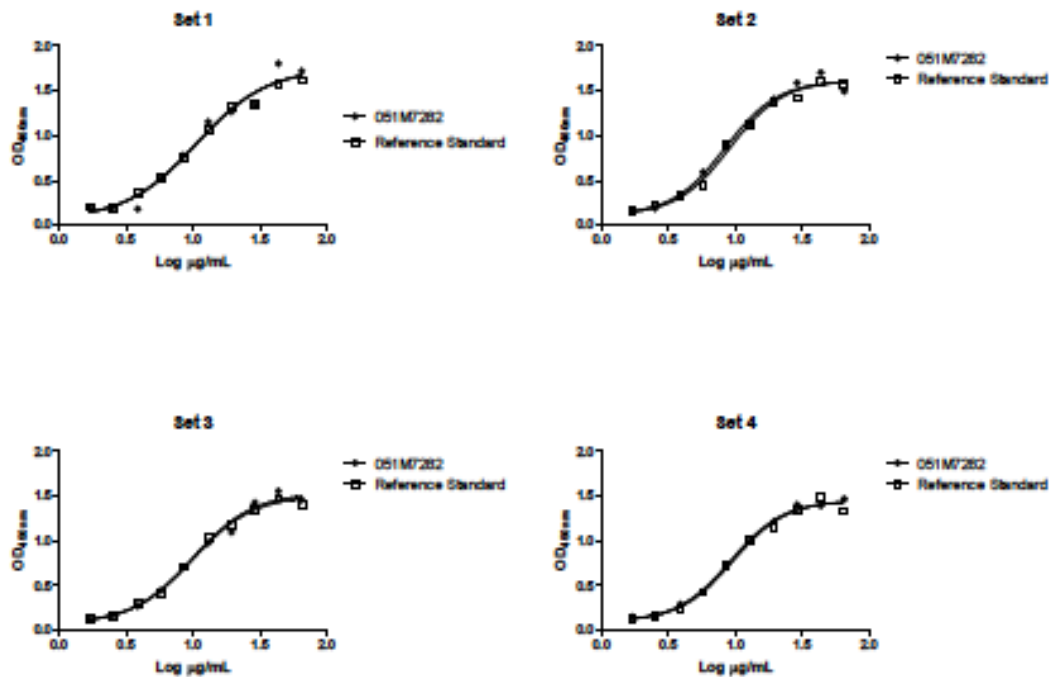


Figure 42. Representative Concentration Curves for mTh2 Polarized T Cell IL-4 ELISA

mTh2 Polarized T cell IL-4 ELISA was done using two independent dilutions (10 points) of Reference Standard (RLD Lot P53514) and the Glatiramer Acetate (Lot 051M7282). Data are expressed as single point measurements tested in 2 separate plates. The geometric mean of the four relative activity values is the final reportable Percent Relative Potency result.

Reviewer comments

These representative data indicate indistinguishable curves in response to Copaxone (RLD Lot P53514) and the Sandoz GA (Lot 051M7282). However, there is published data using a broadly similar mouse splenocyte culture system (discussed above- Bakshi, S, et al. Expert Opin Ther Targets, 17(4):351 - 362 (2013), Towfic, F., et al. PLoS ONE, 9(1): e83757 (2014)). These studies indicate that Copaxone and follow-on products elicit different responses in the expression of many genes. These differences would not be captured by focusing on a single gene (IL-4). Therefore, I recommend that the Sponsor consider expanding their approach to assess expression of a range of genes that may be involved in immune and inflammatory processes relevant to MS disease.

Western Blot with polyclonal antibody

Compares to reference standard

Reviewer comments

Because of the complex nature of GA products, meaningful use of this assay requires visual comparison of bands on the Western blots.

Identity test with Mab panel

Reviewer comments

In this submission, the Sponsor provided a table with positive identity entries. Meaningful interpretation of these data would require tabulation of the signals generated by the different members of the monoclonal antibody panel.

Primary characterization methods

THP-1 chemokine assay

Glatiramer Acetate stimulates APCs (dendritic cells, macrophages, and B cells) to release soluble factors that are believed to alter immune function in MS patients. This proposed biological effect of Glatiramer Acetate is modeled *in vitro* using THP-1 cells. THP-1 cells are a human myeloid cell line that can be differentiated *in vitro* to a monocytic cell capable of presenting antigen. Therefore, the THP-1 Chemokine Assay was developed to model the T cell independent effects of Glatiramer Acetate on APC. This is a quantitative test measuring the synergistic activity of Glatiramer Acetate and IFN- γ to induce the secretion of the IFN- γ -regulated chemokine, monokine induced by interferon-gamma (MIG), from THP-1 cells. THP-1 cells are stimulated with Glatiramer Acetate Injection or the RLD in the presence a sub-optimal concentration of IFN- γ and the amount of MIG secreted over a 24-hour period is quantified by ELISA.

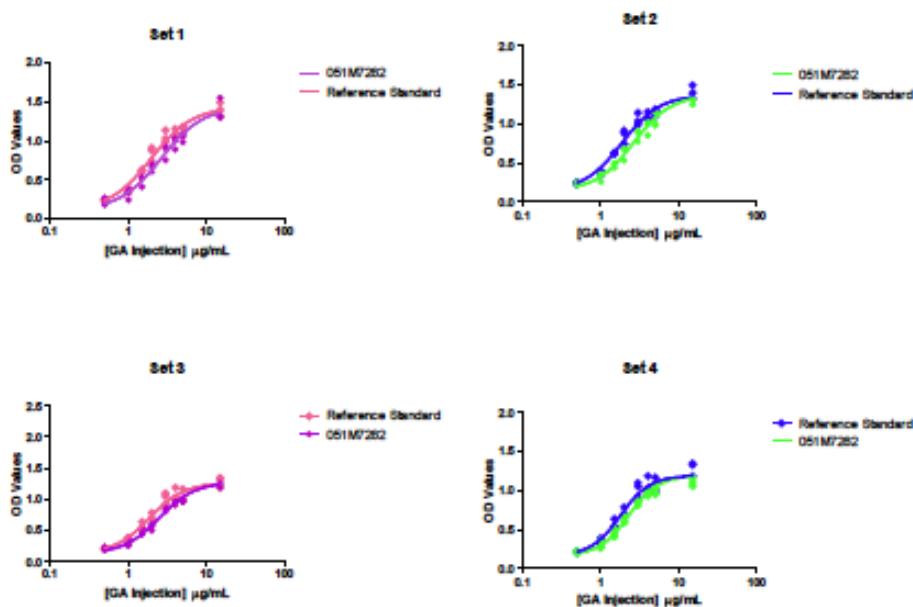


Figure 43. Representative Concentration Curves for THP-1 Chemokine Assay

The reference standard is Lot Copaxone CM9-279.

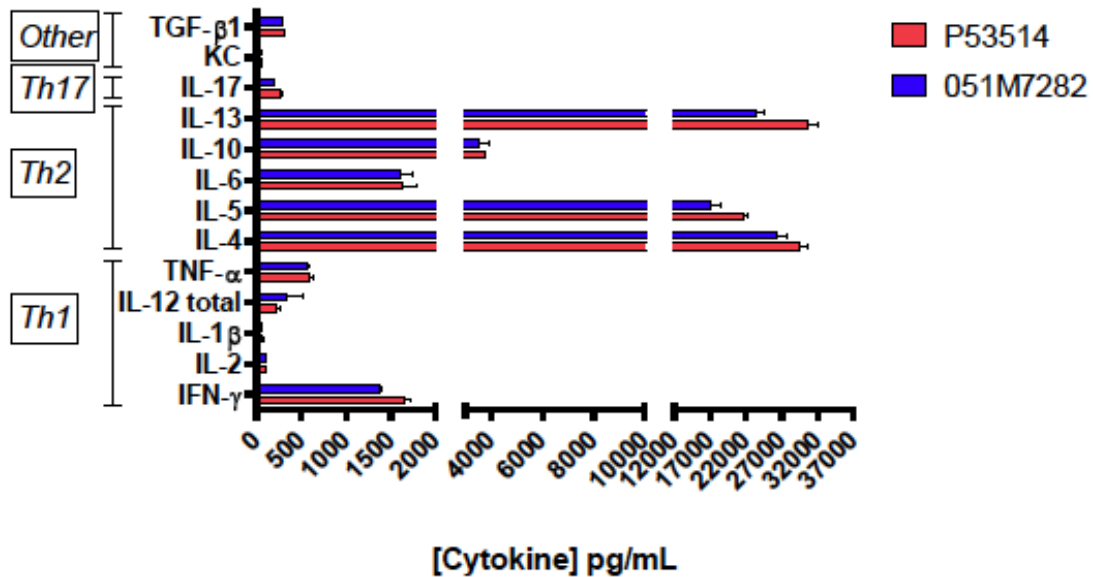
Reviewer comments

Similar considerations apply to those discussed for the murine Th2 cell/ IL-4 assay; i.e. Copaxone and follow-on products may elicit different responses in the expression of many genes, and these differences would not be captured by focusing solely on MIG gene expression. I would also note that the criteria for choosing the Copaxone reference Lot

CM9-279 are not discussed in Sandoz/Momenta's submission, so it is unclear how representative this lot is of TEVA's Copaxone manufacturing.

Generation of Murine Th2 Polarized T Cells

This is an *in vivo/ex vivo*, semi-quantitative test measuring the ability of Glatiramer Acetate to induce the polarization of naïve T cells towards a Th2 phenotype as assessed by multiplexed analyses of Th1-, Th2-, and Th17-associated and other cytokines. Balb/c mice were immunized with Glatiramer Acetate Injection or the RLD, and the draining inguinal lymph nodes were harvested at Day 11 post immunization. Single cell suspensions were made from these lymph node cells and the CD4+ T cell population was isolated by negative immunomagnetic selection. Glatiramer Acetate-reactive T cells were generated through two rounds of re-stimulation *ex vivo* with Glatiramer Acetate Injection or RLD presented by T cell depleted mitomycin c treated APCs. The polarization of Glatiramer Acetate-specific T cells towards a Th2 phenotype was assessed by multiplexed analysis of Th1-, Th2- and Th17-associated cytokines using Enhanced Chemiluminescence technology, and a sandwich ELISA for TGF- β 1. As each polarized cell line is unique, only a semi-quantitative comparison of the degree of Th2 polarization of RLD-reactive and Glatiramer Acetate Injection-reactive T cells can be made.



In ANDA 090218, Amendment 043, Sandoz/Momenta provided data for cytokine profiling from 15 Sandoz/Momenta lots, and 9 Copaxone lots, as summarized in the following figure

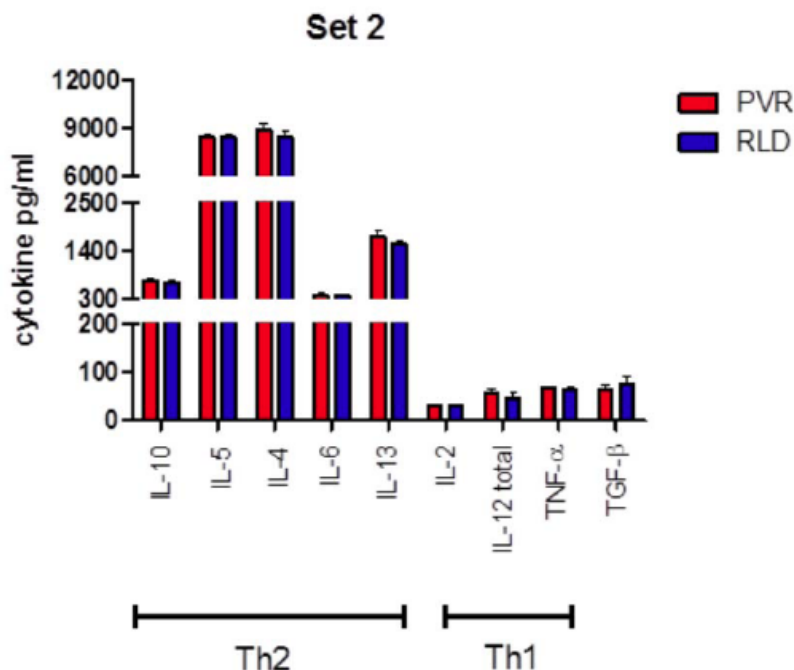


Figure 6-34. Comparison of Cytokine Levels Secreted by Sandoz/Momenta Lots of Glatiramer Acetate and RLDs: Set 2 on Plate 2. PVR lots are Sandoz/Momenta Glatiramer Acetate lots produced during the validation of Process M356-Process-1.1.0.

Reviewer comments

This assay measures 13 different cytokines, and captures reproducibility across a substantial set of Sandoz/Momenta (15 lots) and Copaxone (10 lots). Therefore, in contrast to the assays mentioned above that measure only IL4 or MIG, this assay provides a broader (and therefore more informative) picture of responses elicited by GA product in Th2 T cells, which are important for the mechanism of action. However, as the sponsor states, there may be considerable variability in responses due to variability in the way the cells are isolated and handled. To strengthen the power of this analysis, sources of variability should be identified and minimized. Moreover, in assessing the T cell response, in addition to cytokine expression it will be helpful to assess difference in expression of other genes such as TLRs and chemokines that are important for T cell function, and therefore may bear on the mechanism of action.

Anti-Glatiramer Acetate Antibody Response

SJL/J mice are immunized with Glatiramer Acetate Injection or the RLD over a period of 28 days. Serum is obtained at Day 0, Day 7, Day 14 and Day 28 and tested for the presence of anti-Glatiramer Acetate antibodies by ELISA. The titer of the anti-Glatiramer Acetate antibodies is determined using serial dilutions of the serum. The isotype of the antibody response is determined with isotype-specific antibodies. In addition, the antigenic epitopes present on Glatiramer Acetate Injection and the RLD are compared by assessing the reactivity of Glatiramer Acetate Injection with antibodies generated against the RLD, and vice versa. The dominant isotype of the antibody

response reflects the modulation of the immune response by Glatiramer Acetate towards a Th2 type response

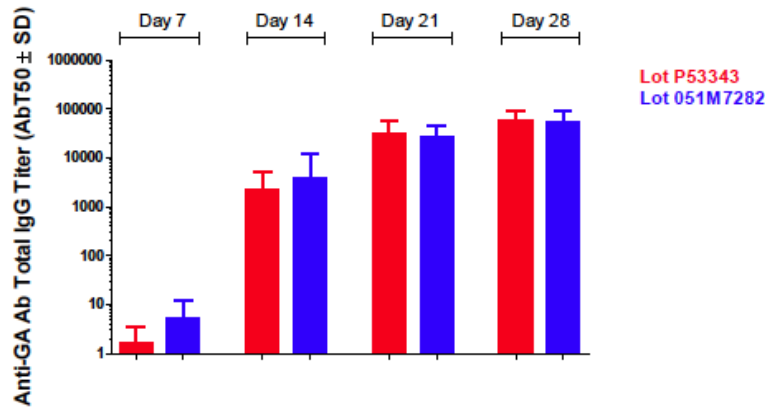


Figure 47. Anti-Glatiramer Acetate Antibody Titer

Serum samples from each mouse were tested in 8 dilutions (range 1:50 to 1:1,024,000, depending on the time point) for total IgG. The antibody titers for individual animals in RLD (Lot P53343) and Glatiramer Acetate (Lot 051M7282) treatment groups at 50% OD₄₅₀ nm (AbT₅₀) were obtained from the nonlinear fit calculations. A one-way ANOVA followed by Tukey's multiple comparisons test (significance level, p<0.05) was used to compare the mean antibody titres (AbT₅₀) at Days 7, 14, 21 and 28.

Sera samples (Day 28) from mice immunized with RLD (Lot P53343) or Glatiramer Acetate (Lot 051M7282) generated a robust antibody titer which cross reacted equally with both antigens within each individual animal.

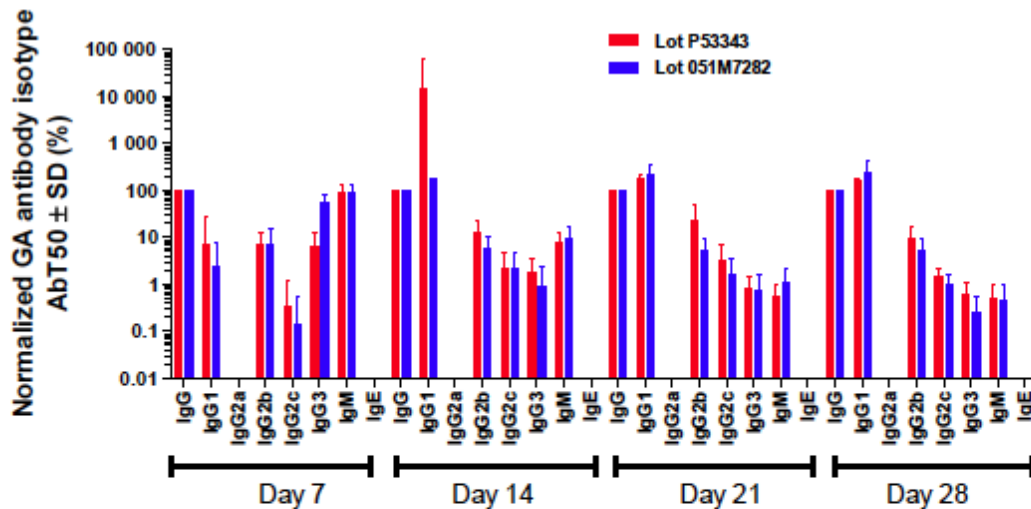


Figure 49. Anti-Glatiramer Acetate Antibody Isotyping: Anti-Glatiramer Acetate Antibody Titer

Serum samples (Day 28) from each mouse were tested in 8 dilutions (range 1:50 to 1:1,024,000, depending on the time point) for total IgG and seven isotypes (IgG₁, IgG_{2a}, IgG_{2b}, IgG_{2c}, IgG₃, IgM and IgE). The antibody isotype titers for individual animals in the RLD (Lot P53343) and Glatiramer Acetate (Lot 051M7278) treatment groups at 50% OD₄₅₀ nm (AbT₅₀) were obtained from the nonlinear fit calculations. The AbT₅₀ values are normalized to total IgG for comparative purpose. A one-way ANOVA followed by Tukey's multiple comparison test (significance level, p<0.05) was used to compare the mean antibody isotype titers (AbT₅₀) for each isotype induced by Glatiramer Acetate (Lot 051M7278) to the RLD (Lot P53343)

Reviewer comments

This assay captures in vivo the distribution of anti-glatiramer antibody isotypes.. The most highly expressed isotype after prolonged culture is IgG1, which is the mouse isotype (together with IgE) that is stimulated by Th2 cells. Thus these data are consistent with an expected GA induction of a Th2 response, and by this criterion, there is no difference between Copaxone and the Sandoz glatiramer product. Switching to the human IgG4 isotype) is induced by Th2 cytokines (Gascan et al., 1991, J Immunol. 147, 8-13, Izizaka et al, 1990 Clin. Exp. Immunol. 79, 392–396.) In Copaxone –treated MS patients anti-GA IgG4/IgG2 and IgG4/IgG1 ratios were inversely correlated with the annualized relapse rate only in the long-term treated patients (> 2 years, mean treatment time of 6.6±3.4 years) vs. patients treated < 2 years--Karussis et al, 2010, J. Neuroimmunology,220, 125-130). Therefore, the human IgG4 response has the potential to be a biomarker of for Th2-based efficacy. However, the transition to this human Th2 isotype is seen after long term dosing (9 months Basile et al, 2006, 177, 161-166) and this aspect of treatment has been not replicated by the mouse antibody model, because this was a short term (28 day) study.

EAE models

Sandoz/Momenta held a teleconference with the FDA on May 24, 2012 related to experimental autoimmune/allergic encephalomyelitis (EAE) animal models for ANDA 090218 for Glatiramer Acetate Injection. The outcomes of this teleconference are summarized in meeting minutes and highlighted below:

1. The FDA agreed that efficacy data from three EAE models are sufficient to establish equivalence with the Reference Listed Drug (RLD). The three EAE models are listed below:

a) Prophylactic dosing using active immunization with Proteolipid Peptide (PLP₁₃₉₋₁₅₁) in the SJL/J strain of mice

Relapsing -remitting model, 25-40 day duration (if extended in 2nd relapse peak)

b) Prophylactic dosing using active immunization with Myelin Oligodendrocyte Glycopeptide (MOG₃₅₋₅₅) in the C57blk/6 strain of mice

Chronic progressive model

c) Therapeutic dosing using the adoptive transfer model with Proteolipid Peptide (PLP₁₃₉₋₁₅₁) in the SJL/J strain of mice.

This model is used to study the effector state of EAE, independently of the immunization phase. Female SJL donor mice are immunized and used as a source of encephalitogenic T cells. Once donor mice have developed an immune response to PLP₁₃₉₋₁₅₁, they are sacrificed and their spleens and lymph nodes harvested. Spleen and lymph node cells are cultured in the presence of PLP₁₃₉₋₁₅₁ to activate encephalitogenic T cells, which are then transferred to female SJL recipient mice to induce EAE. GA treatments are initiated at day 0 of this stage.

Table 5. Summary of Comparative EAE Studies Done with Drug Substance (Lot 051M7282)

Study Description	Dosing Regimen	Comparator RLD Lot	Number of independent studies	Data Reference
Active immunization with PLP ₁₃₉₋₁₅₁ in SJL/J strain with clinical scores as readout	Prophylactic (single dose, 250 µg in emulsion)	P53343	3	Section 3.2.S.3.1.6.4.3 (SN0045)
Active immunization with MOG ₃₅₋₅₅ in C57Blk/6 strain with clinical score as readout	Prophylactic (single dose, 500 µg in emulsion)	P53514	1	Section 3.2.S.3.1.6.4.3 (SN0045)
Active immunization with MOG ₃₅₋₅₅ in C57Blk/6 strain, one study with clinical score and histological analysis as readouts	Prophylactic (single dose, 500 µg in emulsion)	X05071	1	Current document
Adoptive transfer with splenocytes from PLP ₁₃₉₋₁₅₁ immunized mice in SJL/J strain with clinical score as readout	Therapeutic (with 2 mg QD sc dosing for 10 doses)	X05071	1	Current document

MOG 35-55 active immunization /prophylactic dosing study in C57Blk/6 with clinical score and histological analysis as readout

Experimental Design: On Day 0, C57blk/6 mice were immunized with a single sc injection of 200 µg of MOG₃₅₋₅₅ emulsified with CFA/mannitol. Injections were distributed over 2 dorsal sites. For Groups 2 and 5, 500 µg of RLD (Lot X05071) was added to the encephalitogenic emulsion. For Groups 3 and 6, 500 µg of Drug Substance (Lot 051M7282) was added to the encephalitogenic emulsion.

Results: Scores for each group recorded and averaged as a function over time (28 days). The Clinical Score (mean ± SEM) results are shown in [Figure 2](#). As indicated, animals treated with the encephalitogenic emulsion (Group 1, MOG in vehicle) develop symptoms between Day 7 and 14. Treatment with a single dose of RLD (Lot X05071) or Drug Substance (Lot 051M7282) during the immunization delayed the onset of the clinical symptoms and decreased the magnitude of the Clinical Score

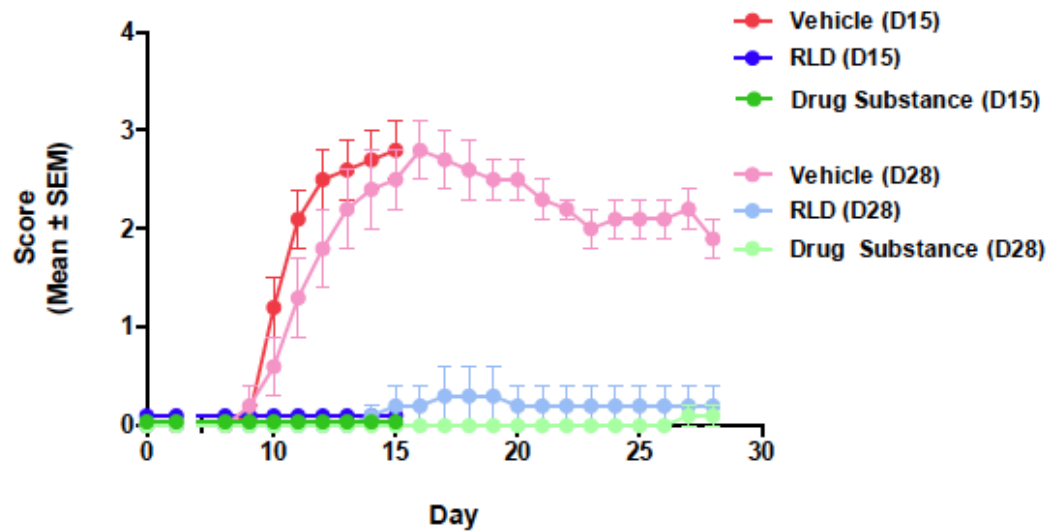


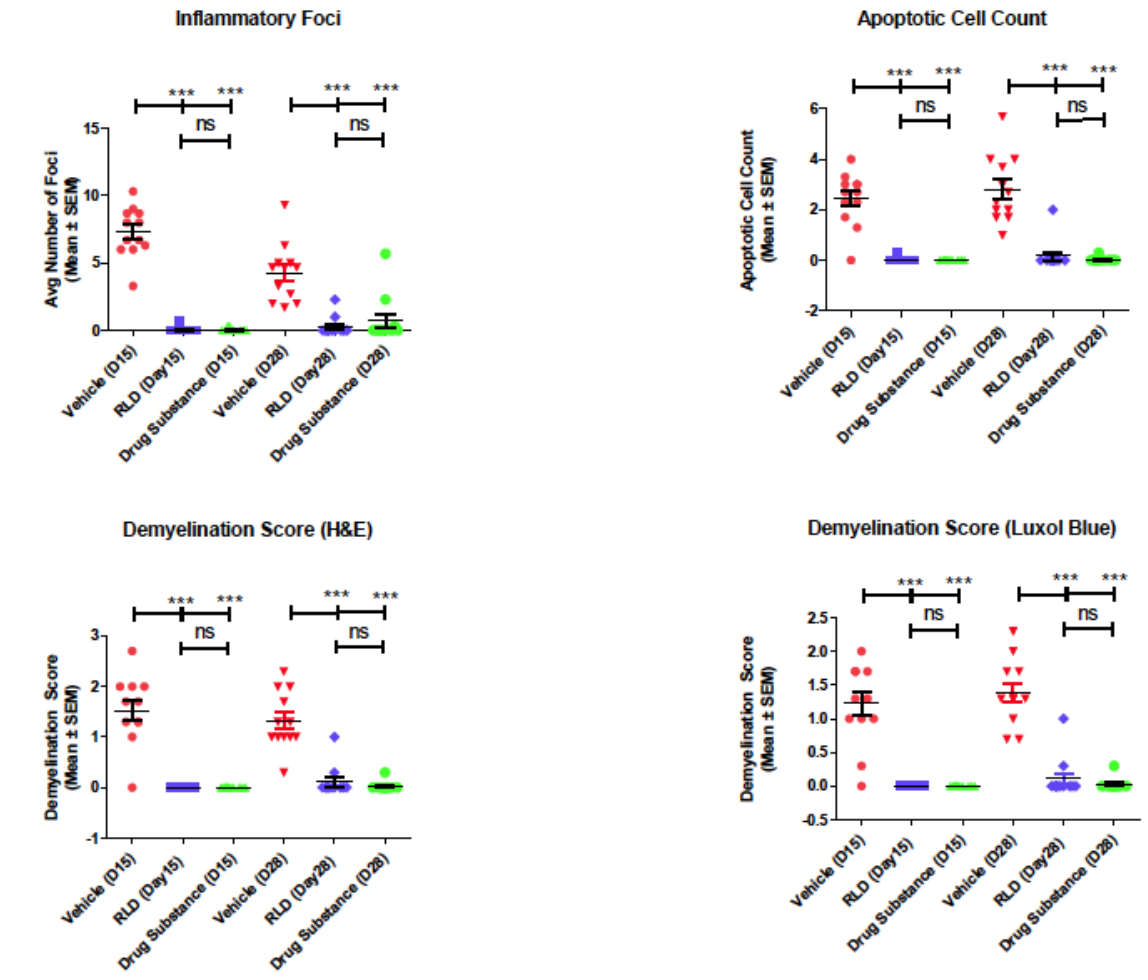
Figure 2. Clinical Scores in Active Immunization (MOG) Model

RLD (Lot X05071, treatment Group 5) and Drug Substance (Lot 051M7282, treatment Group 6), inhibit MOG₃₅₋₃₅ induced EAE in C57Bl/6 mice similarly. A description of the treatment groups is provided in Table 3. The Clinical Scores as a function of time (days) for are shown. Data are expressed as mean \pm SEM with 12 animals in each group. Groups 1 through 3 were sacrificed at Day 15 (peak of disease) and Groups 4 through 6 were sacrificed at Day 28 (end of study) for histological analysis.

There were no significant differences between RLD and Drug Substance in terms of Disease Intensity, Mean Peak Score, or Mean Day Onset on Day 15 or 28 ($p > 0.05$).

Histological Results:

Figure 3 is a graphical representation of the results obtained from the histological analysis performed on Days 15 and 28 comparing inflammatory foci, apoptotic cells, and demyelination (Luxol Blue and H&E) between the Disease Controls (Groups 1 and 4) and the RLD treated mice (Groups 2 and 5) and Drug Substance treated mice (Group 3 and Group 6) at each time point. There were no significant differences between RLD and Drug Substance. Treated groups were compared to the respective Disease Control mice for each time point by one-way ANOVA followed by Tukey's multiple comparison test. Results show highly significant reductions in inflammatory foci, demyelination, and apoptosis with RLD (Lot X05071) treatment ($p < 0.001$) and Drug Substance (Lot 051M7282) treatment ($p < 0.001$) at both time points



Reviewer comments

The data presented for the EAE MOG 35-55 peptide model show no difference between Copaxone and the Sandoz/Momenta GA product

Adoptive Transfer Model

Technical note on FTY720 (Fingilomod)

This is a derivative of ISP-1 (myriocin), a fungal metabolite of the Chinese herb *Iscaria sinclarii* as well as a structural analog of sphingosine. It is a novel immune modulator that prolongs allograft transplant survival in numerous models by inhibiting lymphocyte emigration from lymphoid organs. In the adoptive transfer model, it is used as a kind of control, to completely abrogate the EAE response, as see below.

Results: The clinical symptoms of EAE progression were monitored daily and Clinical Scores for each group recorded and averaged as a function over time (28 days). All animals adoptively transferred with splenocytes from PLP immunized donor mice and treated with vehicle (Group 1, vehicle control) developed symptoms between Day 5 and 10. Therapeutic dosing with FTY720 using the oral route, QD, (3 mg/kg, Group 2,

Positive control) for 28 days resulted in complete block of EAE symptoms. Treatment with 2 mg, administered sc QD, starting on Day 0 post-transfer of the encephalitogenic splenocytes (therapeutic dosing regimen) for a duration of 9 days with either RLD (Lot X05071, Group 3) or Drug Substance (Lot 051M7282, Group 4) delayed the onset of the clinical symptoms and decreased the magnitude of the Clinical Scores. The optimal dose (2 mg), day of initiation, and duration of treatment (Day 0-Day 9) were chosen based on data from two pilot studies conducted with RLD.

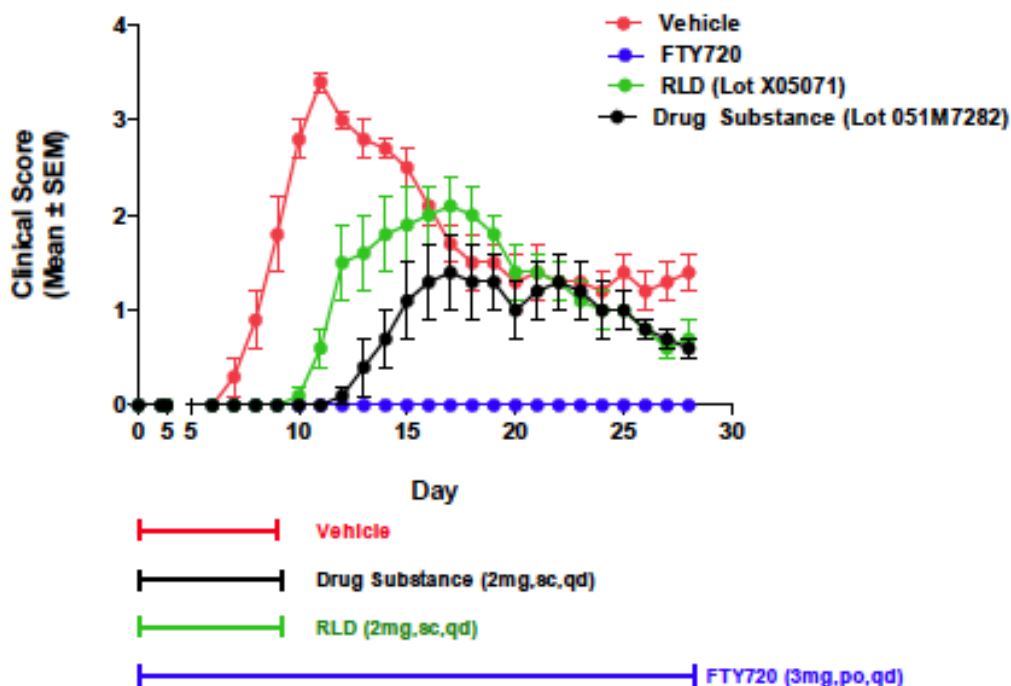


Figure 1. Clinical Scores in Adoptive Transfer Model

RLD (Lot X05071) and Drug Substance (Lot 051M7282) similarly inhibit EAE in SJL/J mice induced by adoptive transfer of splenocytes from PLP₁₃₀₋₁₅₁ immunized mice. A description of the treatment groups is provided in Table 1. The Clinical Scores as a function of time (days) for are shown. Data are expressed as mean ± SEM with 12 animals in each group. The lines at the bottom indicate the type and duration of treatment.

There were no statistically significant differences between RLD and Drug Substance for any of the three parameters: Mean Day Onset, Disease Intensity, and Mean Peak Score. A Mean Peak Ratio of 1.2 supported no significant differences between RLD and Drug Substance.

Reviewer comments

The data presented indicate equivalence with this assay between Copaxone and the Sandoz GA. In fact, the Sandoz product appears to have somewhat greater efficacy, but the Sponsor states this is not statistically significant.

Overall, I agree with the Sponsor that the EAE results do not show a difference between Copaxone and the Sandoz/Momenta product. The importance of EAE models for MS is seen from the fact that the major MS biologics (IFN-β, GA, and anti-VLA-4 antibody)

have show correlation in EAE results and therapeutic efficacy. However, there are many examples of EAE treatment successes, which have not translated into similar MS successes, including IFN- γ , and Myelin-Basic Protein oral tolerance. Perhaps most significant for assessing similarity between GA products is the inability of the EAE models to mirror the long-term beneficial immunological modulation that is an important aspect of EAE therapy. Therefore, I find that the while similar results for Copaxone and Sandoz GA seen in EAE may provide necessary support for comparability, by themselves they are not sufficient to provide assurance that the two products will have similar safety and efficacy profiles in the treatment of human MS.

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From: "Kozlowski, Steven" <Steven.Kozlowski@fda.hhs.gov> **Date:** Fri, 6 Jun 2014 17:01:12 -0400 **To:** "Rosenberg, Amy" <amy.rosenberg@fda.hhs.gov>, Fred Mills <frederick.mills@fda.hhs.gov>, "Verthelyi, Daniela I" <Daniela.Verthelyi@fda.hhs.gov> **Subject:** RE: Copaxone generics

Some thoughts on the recommendations

I am also including the summary from the draft OCP DARS review below:

Summary

Teva has conducted a nonclinical gene expression study intended to benchmark the pharmacology and mechanism of action of glatiramer acetate (GA, Copaxone®) in comparison to a generic glatiramer (b) (4) (Natco Pharma Ltd). This study has been published in two peer-reviewed publications (Bakshi et al. 2013; Towfic et al. 2014) and the gene expression data are available in the Gene Expression Omnibus (GEO) database under Accession #GSE40566. This consult is based on a critical review and re-analysis of those data, and includes a critical assessment of study design, microarray data quality and gene expression data interpretation. Our review determined that the basic experimental design is not appropriate for product comparisons, and that the results generated from this study would be problematic if used as a basis for considering the biological sameness of a generic product versus a reference listed drug. We conclude the following: (a) study design weaknesses make it difficult to draw unambiguous conclusions about possible MOA and targets suggested by gene expression data; (b) the Teva dataset contains significant bias in signal intensity due to sample processing that is not completely eliminated by batch adjustment methods and therefore may confound certain types of analyses and comparisons of within-sample variability; and (c) re-analysis of the GEO data set suggests that, based on this study, the Teva and Natco products can be considered to have very similar

effects on the efficacy-related pathways proposed for GA's mechanism of action as elucidated by the pathway analysis of the available gene expression data. We further conclude that there are no reliable differences between the reference listed drug and the generic samples used in the reported study, and that the differences described cannot be considered relevant to product safety or efficacy.

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/s/

SIMON S ENG
06/13/2014

OGD SCIENCE STAFF CONSULT REVIEW

To: Jing Li, Ph.D., Staff Fellow, Peptide Team, OGD

Re: ANDA 090218

Consult No: N/A

Drug Product: Glatiramer Acetate Injection
20 mg/ml

Sponsor: Sandoz Inc

Original Submission: July 20, 2011, Aug 09, 2011, March 23, 2012 (Amendment 0022, 0023, 0038)

Date of Consult Request: November 09, 2012

Date of Review: November 19, 2012

Consultant: Bhawana Saluja, Ph.D.
Science Staff, OGD

Robert Lionberger, Ph.D.
Science Staff, OGD

Through: Lawrence X. Yu, Ph.D.
Deputy Director for Science and Chemistry, OGD

Reason for Consultation

Input to the questions raised by Sandoz/Momenta (SM) in ANDA # 090218.

Background Summary

Copaxone (NDA # 02-0622) is the brand name for glatiramer acetate (formerly known as copolymer-1), and was approved by the FDA on December 20, 1996. Copaxone is supplied as a single-use prefilled syringe containing 1 mL of a clear, colorless to slightly yellow, sterile, non-pyrogenic solution containing 20 mg of glatiramer acetate and 40 mg of mannitol in cartons of 30 single-use prefilled syringes with 33 alcohol preps. The recommended dose of Copaxone is 20 mg/day.

Copaxone[®] is indicated for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis, including patients who have experienced a first clinical episode and

have MRI features consistent with multiple sclerosis. The recommended dose of Copaxone[®] for the treatment of Relapsing-Remitting of Multiple Sclerosis is 20 mg *once a day* injected subcutaneously.

Copaxone was originally approved and marketed as a lyophilized powder for injection (Copaxone for Injection). The drug, which is injected daily, was reconstituted by the patient prior to injection. The relevant sections of the product label approved in 1996 including “HOW SUPPLIED” and “INSTRUCTIONS FOR INJECTING COPAXONE[®]” are provided in Appendix A. There was no mention of (b) (4). The product was supplied with both 1 and 3 cc syringes; 3 cc syringe for reconstitution and 1 cc syringe for injection.

(b) (4)

On May 21, 2001, Teva submitted a supplement for introduction of a pre-filled syringe (Copaxone[®] injection). The pre-filled syringe contained the same inactive ingredients, at the same levels, as a reconstituted form of the approved lyophilized product. This supplement was issued an approvable letter by the FDA on September 21, 2001.

(b) (4)

1. (b) (4)

2. (b) (4)


(Appendix C).

Response to questions:


Regulatory Pathway (From ANDA # 090218)

1. *Does the agency agree that the reference product, for the purposes of ANDA approval, is Copaxone[®] (glatiramer acetate) solution for subcutaneous injection provided as a single-use, pre-filled glass syringe containing a single dose of 20 mg of glatiramer acetate?*

Response: Yes. Please see Appendix G.

2.  (b) (4)
Does the agency agree?

Response:  (b) (4)
Please see Appendix G.

3.  (b) (4)
Does the Agency concur?

Response: Yes.

4.  (b) (4)

3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020622s057lbl.pdf
4. <http://darrrts.fda.gov> NDA#020622, Annual report 11(\fdswa150\NONECTD\N20622\Y_011\2007-01-31).
5. http://www.copaxone.com/pdfs/Injecting_Guide.aspx

(b) (4) of the generic glatiramer acetate in ANDA 90218?

Response: OGD will not review or comment on the (b) (4) that the firm proposes to use. Please follow the procedure for approval stated in question 3.

Life Cycle Management (From ANDA # 090218)

5. (b) (4)
Does the Agency agree?

Response: Yes

6. (b) (4)

Response: (b) (4)

Additional Questions by OGD Chemistry Reviewer

7. Is Sandoz proposed (b) (4) based on the information submitted?

Response: (b) (4)
or the purpose of ANDA approval. (Appendix G)

Although not required for ANDA approval purposes, below is the review of (b) (4)

Sandoz provided a (b) (4) upon OGD's request.

8.

9. *Is there any additional information required?*

Response: No

Conclusions:

In conclusion,

(b) (4)

(b) (4)

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SIMON S ENG
06/18/2013

BHAWANA SALUJA
06/18/2013

ROBERT A LIONBERGER
06/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 090218

PROPRIETARY NAME REVIEWS

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	February 26, 2015
Application Type and Number:	ANDA 090218
Product Name and Strength:	Glatopa (glatiramer acetate injection) 20 mg/mL, 1 mL prefilled syringe
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sandoz Inc.
Panorama #:	2015-49522
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

Contents

1	INTRODUCTION.....	1
1.1	Regulatory History.....	1
1.2	Product Information.....	1
2	RESULTS.....	1
2.1	Misbranding Assessment.....	2
2.2	Safety Assessment.....	2
3	CONCLUSIONS.....	3
3.1	Comments to the Applicant.....	3
4	REFERENCES.....	4

1 INTRODUCTION

This review evaluates the proposed proprietary name, Glatopa, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an external name study, conducted by [REDACTED] (b) (4), for this product.

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Glatopa, on November 3, 2011. The Division of Medication Error Prevention and Analysis (DMEPA) found the name, Glatopa, acceptable in OSE Review #2011-4269 and 2011-4270, dated January 17, 2013.

The goal date for approval of this application is March 1, 2015. Given the amount of time that has elapsed since our previous review, we requested that the applicant resubmit the name, Glatopa, for our review.

1.2 PRODUCT INFORMATION

The following product information is provided in the February 20, 2015 proprietary name submission.

- Intended Pronunciation: gluh-TOH-puh
- Active Ingredient: Glatiramer Acetate
- Indication of Use: Reduction of the relapse frequency in patients with Relapsing-Remitting Multiple Sclerosis
- Route of Administration: Subcutaneous injection
- Dosage Form: Injection
- Strength: 20 mg/mL
- Dose and Frequency: 20 mg (1 mL) once daily
- How Supplied: Glatopa is supplied as a 1 mL single dose glass syringe with attached 1/2 inch length 29-gauge needle. Each syringe contains 1 mL. Each prefilled syringe is contained in a blister and supplied in cartons containing 30 syringes and 34 alcohol preps.
- Storage: 2° to 8°C (36° to 46°F)
- Reference Listed Drug: Copaxone (glatiramer acetate injection), NDA 020622

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Neurology Products (DNP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name¹.

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Glatopa, "is not derived from any one particular concept." This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 FDA Name Simulation Studies

Ninety-three practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Thirteen participants in the outpatient study misinterpreted the beginning letter "G" as the letter "C". Five participants in the inpatient study misinterpreted the beginning letter "G" as the letter "P". Six participants in the verbal study misinterpreted the first letter "a" in Glatopa as the letter "i". Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, February 24, 2015 e-mail, the Division of Neurology Products (DNP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

¹USAN stem search conducted on February 22, 2015.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Table 1 lists the number of names with the combined orthographic and phonetic score of $\geq 50\%$ retrieved from our POCA search² organized as highly similar, moderately similar or low similarity for further evaluation. Table 1 also includes names identified by

(b) (4)

Table 1. POCA Search Results	Number of Names
Highly similar name pair: combined match percentage score $\geq 70\%$	1
Moderately similar name pair: combined match percentage score $\geq 50\%$ to $\leq 69\%$	88
Low similarity name pair: combined match percentage score $\leq 49\%$	10

2.2.6 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 99 names contained in Table 1 determined all 99 names will not pose a risk for confusion as described in Appendices C through H.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have further questions or need clarifications, please contact Kevin Wright, OSE Project Manager, at 301-796-3621.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Glatopa, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your February 20, 2015 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

² POCA search conducted on February 21, 2015.

4 REFERENCES

1. *USAN Stems* (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page>)

USAN Stems List contains all the recognized USAN stems.

2. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

3. *Drugs@FDA*

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present.

Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see *Drugs @ FDA Glossary of Terms*, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

4. *RxNorm*

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm

(<http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#>).

5. *Division of Medication Errors Prevention and Analysis Proprietary Name Consultation Requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment:** For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNCE. OPDP or DNCE evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNCE provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.³

³ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there medical and/or coined abbreviations in the proprietary name?
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

- b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@FDA, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:
- Highly similar pair: combined match percentage score $\geq 70\%$.
 - Moderately similar pair: combined match percentage score $\geq 50\%$ to $\leq 69\%$.
 - Low similarity: combined match percentage score $\leq 49\%$.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names with overlapping or similar strengths or doses represent an area for concern for FDA. The dosage and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and it can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form, etc.) may be limited when the strength or dose overlaps. We review such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

- c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

- d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is $\geq 70\%$).

<u>Orthographic Checklist</u>		<u>Phonetic Checklist</u>	
Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more letters.</i>	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as <i>z</i> and <i>f</i>), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is $\geq 50\%$ to $\leq 69\%$).

<p>Step 1</p>	<p>Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation.</p> <p>For single strength products, also consider circumstances where the strength may not be expressed.</p> <p>For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components.</p> <p>To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion:</p> <ul style="list-style-type: none"> ○ Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. ○ Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. ○ Similar sounding doses: 15 mg is similar in sound to 50 mg
<p>Step 2</p>	<p>Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.</p>

<p>Orthographic Checklist (Y/N to each question)</p> <ul style="list-style-type: none"> • Do the names begin with different first letters? <p>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</p> <ul style="list-style-type: none"> • Are the lengths of the names dissimilar* when scripted? <p>*FDA considers the length of names different if the names differ by two or more letters.</p> <ul style="list-style-type: none"> • Considering variations in scripting of some letters (such as <i>z</i> and <i>f</i>), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted? 	<p>Phonetic Checklist (Y/N to each question)</p> <ul style="list-style-type: none"> • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?
--	--

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is $\leq 49\%$).

In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where, for example, there are data that suggest a name with low similarity is nonetheless misinterpreted as a marketed product name in a prescription simulation study. In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Glatopa Study (Conducted on February 20, 2015)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u></p> <p><i>Glatopa 20mg subcutaneously once daily</i></p>	<p>Glatopa</p> <p>Inject 20 mg subcutaneously once daily</p>
<p><u>Outpatient Prescription:</u></p> <p><i>Glatopa</i> <i>20mg SQ qd</i> <i>#30</i></p>	<p>Disp. #30</p>

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

				251 People Received Study
				93 People Responded
Study Name: Glatopa				
Total	34	25	34	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
BLATAPA	0	0	1	1
BLATAPIR	0	0	1	1
CLATOPA	4	1	0	5
CLATOPA (OR GLATOPA)	1	0	0	1
CLETOPA	2	0	0	2
CLOTOPA	5	0	0	5
CLOTOPS	1	0	0	1
ELATOPIA	0	0	1	1
FLATOPIA	0	0	1	1
GLATAPA	0	0	6	6
GLATOPA	8	12	16	36
GLATOPIA	0	0	3	3
GLATOPO	1	0	0	1
GLATOPO 20MG	1	0	0	1
GLATOPS	1	0	0	1
GLAUTOPA	0	1	0	1
GLETOPA	1	2	0	3
GLITOP	0	1	0	1
GLITOPA	0	5	0	5
GLOTOPA	8	1	0	9
GLOTOPS	1	0	0	1
GLUTOPA	0	2	0	2
PLATOPA	0	0	5	5

Appendix C: Highly Similar Names (e.g., combined POCA score is $\geq 70\%$)

No.	Proposed Name: Glatopa Established name: Glatiramer Acetate Dosage form: Injection Strength: 20 mg/mL Usual Dose: 20 mg (1 mL) subcutaneously once daily	POCA Score (%)	Orthographic and/or phonetic differences in the names sufficient to prevent confusion Other prevention of failure mode expected to minimize the risk of confusion between these two names.
1.	Glatopa	100	This name is the subject of this review.

Appendix D: Moderately Similar Names (e.g., combined POCA score is $\geq 50\%$ to $\leq 69\%$) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
1.	Glutol	58
2.	(b) (4)***	55
3.	Glutamic-500	54
4.	Glauctabs	50

Appendix E: Moderately Similar Names (e.g., combined POCA score is $\geq 50\%$ to $\leq 69\%$) with overlap or numerical similarity in Strength and/or Dose

No.	Proposed Name: Glatopa Established name: Glatiramer Acetate Dosage form: Injection Strength: 20 mg/mL Usual Dose: 20 mg (1 mL) subcutaneously once daily	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
1.	(b) (4)***	69	The infixes/suffixes of this name pair have sufficient orthographic differences The first/second/third syllables of this name pair sound different.
2.	Glassia	62	The infixes/suffixes of this name pair have sufficient orthographic differences The second/third syllables of this name pair sound different.
3.	Glaucou	59	The infixes/suffixes of this name pair have sufficient orthographic differences The second syllable of this name pair sound different. Glatopa contains an extra syllable.
4.	Glucose	58	The suffixes of this name pair have sufficient orthographic differences The first syllable of this name pair sound different. Glatopa contains an extra syllable.
5.	Glytuss	57	The infixes/suffixes of this name pair have sufficient orthographic differences The first/second syllables of this name pair sound different. Glatopa contains an extra syllable.
6.	Glatiramer	53	The infixes/suffixes of this name pair have sufficient orthographic differences The second/third syllables of this name pair sound different. Glatiramer contains an extra syllable.

No.	Proposed Name: Glatopa Established name: Glatiramer Acetate Dosage form: Injection Strength: 20 mg/mL Usual Dose: 20 mg (1 mL) subcutaneously once daily	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
7.	Grastek	52	The infixes/suffixes of this name pair have sufficient orthographic differences The first/second syllables of this name pair sound different. Glatopa contains an extra syllable.
8.	(b) (4)***	51	The suffixes of this name pair have sufficient orthographic differences The first/third syllables of this name pair sound different.

Appendix F: Low Similarity Names (e.g., combined POCA score is $\leq 49\%$)

No.	Name	POCA Score (%)
1.	Glucagon	49
2.	Claforan	48
3.	Glipizide	44
4.	Methyldopa	44
5.	Topamax	38
6.	Citalopram	32
7.	Zolpidem	28
8.	Keppra	26
9.	Levodopa/Carbidopa	25
10.	Insulin Glargine	17

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
1.	Glau-Opt	62	The product characteristics were not found in commonly used (or external) databases.
2.	Gladase	60	This product has been discontinued. It contained papain. Topical products containing papain are not FDA approved. The FDA has ordered all companies to stop manufacturing topical products containing papain as of November 24, 2008 and they must not be shipped after January 21, 2009. After this time, all topical products containing papain must obtain FDA approval prior to resuming manufacturing or shipping.
3.	Gladase-C	60	This product has been discontinued. It contained papain. Topical products containing papain are not FDA approved. The FDA has ordered all companies to stop manufacturing topical products containing papain as of November 24, 2008 and they must not be shipped after January 21, 2009. After this time, all topical products containing papain must obtain FDA approval prior to resuming manufacturing or shipping.
4.	Glaucol	56	The product characteristics were not found in commonly used (or external) databases.
5.	Glytone	56	Glytone is a family tradename for multiple topical products (e.g., cream, gel, lotion, body wash, and toner); therefore, the dosage form would have to be specified on a prescription. There are no dosage form overlaps between Glytone and Glatopa.
6.	Glutaral	52	The product characteristics were not found in commonly used (or external) databases.
7.	Glutamate	51	Glutamate is a chemical neurotransmitter. We did not identify any drug that has this name.
8.	Galactose	50	Galactose is a monosaccharide sugar. It can be purchased for pharmaceutical compounding. We did not identify any finished drug products that have this name.

Appendix H: Names not likely to be confused due to notable spelling, orthographic and phonetic differences.

No.	Name	POCA Score (%)
1.	Latuda	62
2.	Gelato	60
3.	Glumetza	60
4.	Larodopa	60
5.	Glister	58
6.	Glyset	58
7.	Salitop	58
8.	Glycate	56
9.	Glycophos	56
10.	Glycort	56
11.	Gly-Cort	56
12.	Glycoprep	54
13.	Levodopa	54
14.	Madopar	54
15.	Parcopa	54
16.	Platet	54
17.	Catosal	53
18.	(b) (4)***	53
19.	Platosin	53
20.	Atopalm	52
21.	Atopica	52
22.	Brocadopa	52
23.	E-Glades	52
24.	Gelatin	52
25.	Gen-Lanta	52
26.	Glucoscan	52
27.	Glydo	52

No.	Name	POCA Score (%)
28.	Glyoxal	52
29.	(b) (4)***	52
30.	Protopam	52
31.	Gallopamil	51
32.	Glucophage	51
33.	Tritop	51
34.	Bendopa	50
35.	Blood Stop	50
36.	Carbidopa	50
37.	Carbodopa	50
38.	(b) (4)***	50
39.	Glucamet	50
40.	Glucose	50
41.	Glucotrol	50
42.	Glycron	50
43.	(b) (4)***	50
44.	Yutopar	50
45.	Balanta	54
46.	Neulasta	53
47.	(b) (4)***	52
48.	Lactocal	52
49.	Mylanta	52
50.	Natroba	52
51.	Placebo	52
52.	Silapap	52
53.	(b) (4)***	51
54.	Clotam	51
55.	Del-Beta	51
56.	Lidopen	51
57.	Quala T LA	51

No.	Name	POCA Score (%)
58.	Betapar	50
59.	(b) (4)***	50
60.	Clopra	50
61.	Dasetta 1/35	50
62.	Dasetta 7/7/7	50
63.	Del-Aqua	50
64.	Dilotab	50
65.	Duratuss A	50
66.	Ignatia	50
67.	Lidopro	50
68.	Solesta	50

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/s/

LORETTA HOLMES
02/26/2015

LUBNA A MERCHANT
02/26/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Proprietary Name, Label, Labeling and Packaging Review--ANDA

Date: January 17, 2013

Reviewer: Aleksander Winiarski, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Jamie Wilkins Parker, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Glatopa (Glatiramer Acetate) Injection, 20 mg/mL,
1 mL pre-filled syringe.

Application Type/Number: ANDA 090218

Applicant/sponsor: Sandoz Inc.

OSE RCM #: 2011-4269 and 2011-4270

*** This document contains proprietary and confidential information that should not be released to the public.***

CONTENTS

1	INTRODUCTION.....	1
1.1	Regulatory History.....	1
1.2	Product Information.....	1
2	RESULTS.....	1
2.1	Promotional Assessment of Proposed Proprietary Name.....	2
2.2	Safety Assessment of Proposed Proprietary Name.....	2
2.3	Safety Assessment of Proposed Labels, Labeling and packaging.....	6
3	CONCLUSIONS.....	6
3.1	DMEPA Comments to the Applicant.....	7
3.2	DMEPA Comments to OGD for the Applicant.....	7
	REFERENCES.....	8
	APPENDICES.....	10

1 INTRODUCTION

This review evaluates the proposed proprietary name, Glatopa (Glatiramer Acetate) Injection, from a safety and promotional perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 REGULATORY HISTORY

The reference listed drug, Copaxone (NDA 020602) Injection, 20 mg/mL was approved on December 20, 1996. Currently, the only marketed formulation of Copaxone is a 1 mL pre-filled syringe. This is the first proposed proprietary name submitted by the Applicant for this ANDA.

1.2 PRODUCT INFORMATION

The following product information is provided in the November 3, 2011 proprietary name submission:

- Active Ingredient: Glatiramer Acetate
- Indication of Use: Reduction of the relapse frequency in patients with Relapsing-Remitting Multiple Sclerosis
- Route of Administration: Subcutaneous injection
- Dosage Form: Injection
- Strength: 20 mg/mL
- Dose and Administration Frequency: 20 mg once daily
- How Supplied: Blister each containing 1 single use pre-filled syringe, 30 blisters per carton
- Storage: Refrigerate at 2°C to 8°C

2 RESULTS

The following sections provide the information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 PROMOTIONAL ASSESSMENT OF PROPOSED PROPRIETARY NAME

The Office of Prescription Drug Promotion (OPDP) determined the proposed name is acceptable from a promotional perspective. DMEPA and the Office of Generic Drugs (OGD) concurred with the findings of OPDP's promotional assessment of the proposed name.

2.2 SAFETY ASSESSMENT OF PROPOSED PROPRIETARY NAME

The following aspects of the name were considered in the safety evaluation.

2.2.1 United States Adopted Names (USAN) SEARCH

The June 14, 2012 United States Adopted Name (USAN) stem search identified that a USAN stem is not present in the proposed proprietary name.

2.2.2 Components of the Proposed Proprietary Name

The Applicant did not indicate in their submission that the proposed name, Glatopa, has a derivation or an intended meaning. This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Medication Error Data Selection of Cases

DMEPA searched the AERS database for medication errors involving the reference listed drug, Copaxone, which would be relevant to this review.

The June 29, 2012 search of the Adverse Event Reporting System (AERS) database used the following search terms: Glatiramer, Glatiramer acetate (active ingredient), Copaxone (trade), Copax% (verbatim), Medication Errors (HLGT), Product Label Issues (HLT), Product Packaging Issues (HLT), and Product Quality Issues NEC (HLT) from the date of our last search March 30, 2010 in OSE RCM# 2010-658 and 2010-632. Our search retrieved 42 reports.

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and contributing factors to the error when provided by the reporter.

After individual review, 28 cases were not included in the final analysis for the following reasons: dose omission due to non-compliance (n=5), adverse reaction unrelated to a medication error (n=7), medication error or overdose related to another drug (n=5), incorrect site of administration not due to medication error [accidentally pricking/injecting the finger (n=2), there was no indication in the cases that patients chose an incorrect injection site)], intentional overdose (n=1), loss or lack of effect unrelated to a medication error (n=2), product quality issue (broken syringe) (n=1), potentially expired drug administered (n=1), accidental storage outside recommended temperature (n=2), and duplicate cases (n=2).

Following exclusions, the search yielded 14 relevant cases. These errors are similar to those previously reviewed in OSE review # 2010-658 and 2010-632.

2.2.3 Medication Error Cases and Analysis

The summaries of the eight medication error cases relevant to Glatopa's label and labeling are below:

Wrong technique leading to accidental exposure (n=1)¹

Nurse attempted to remove air bubbles from the syringe prior to use and accidentally expelled some of the drug from the syringe into her eye. The eye was flushed with water and was not irritated. No other outcomes were provided. The instructions for use state not to expel the air bubble from the syringe before injecting the medicine. No changes to the label are recommended based on this case.

Wrong site and/or route of administration (n=11)²

Two cases report a wrong site of injection.

The first case (ISR 7612070) describes a patient who received the injections by a family member in the mid back area, which is not an approved injection site. The physician stated that these injections were intradermal instead of the approved subcutaneous route of administration. Patient experienced several welts and lesions, some of which have healed. No other outcomes or relevant details were provided in the case.

The second case (ISR 7893317) describes a patient who experienced painful injection site reactions, according to the reporter the patient did not space out the injection sites. Therapy was interrupted and patient used ice for the swelling. No other outcomes or relevant details were provided in the case.

The remaining nine cases describe a wrong route of administration.

The first case (ISR 8450039) describes the incorrectly administered drug via the intradermal route instead of subcutaneously. The patient experienced injection site necrosis. Patient is recovering with complication (scarring), the drug continued and additional training was provided to the patient. No other outcomes were provided.

Two cases describe the incorrectly administered drug via the intramuscular route instead of subcutaneously. In the first case (ISR 8256615) the report described a patient who injected the drug too deeply, which resulted in pain and severe swelling of the leg. No other outcomes were provided. In the second case (ISR 7233571) the nurse suspected that the patient may have been injecting the drug intramuscularly because he experienced pain and tenderness of the bicep after injections. No other outcomes were provided.

¹ ISR number: 7345425

² ISR numbers: 7612070, 8450039, 7893317, 8256615, 7233571, 8295859, 8352222, 7444384, 8107018, 7615661, 788033

The patient information leaflet clearly specifies the correct injection sites, route of administration, and provides direction regarding spacing out the injections. No changes to the label are recommended based on the cases above

Three of the cases describe patients that accidentally injected a vein during dosing with Copaxone (ISRs 8295859, 8352222, and 7444384).

In all three cases, patients experienced adverse reactions including: injection site bleeding, respiratory difficulties, dizziness, facial flushing, loss of consciousness, decreased blood pressure and/or increased heart rate. In two of the cases patients were admitted to the emergency room and hospitalized, although both recovered in 2 hours and in 24 hours respectively. Copaxone therapy was discontinued in one of the cases, and information regarding discontinuation of the drug was not provided in the second case. In the remaining case the patient's symptoms began to subside after approximately 30 minutes and she did not seek any medical attention at the time. The case stated that it has taken the patient one month to recover (symptom unclear) but the patient will restart therapy.

The remaining three cases describe patients that may have injected a vein during dosing with Copaxone (ISRs, 7615661, 8107018 7880033).

Two of the cases describe patients who experienced adverse reactions including: blurred vision, dizziness, loss of motor function, difficulty in breathing, flushing and increased heart rate. In the first case (ISR 7615661) the patient questioned whether she was experiencing an allergic reaction or if she injected her vein. The patient received medical attention in the Emergency Department and the therapy was discontinued. No other details were provided. In the second case (ISR 8107018) the patient suspected that she injected a vein because of the cardiovascular adverse events she experienced, she reported that this was a life-threatening event, however there were no additional details provided in the narrative to suggest she required or obtained medical attention. No additional outcomes were provided. The remaining case (ISR 788033) describes a physician that inquired to the company about expected adverse reactions if a patient injected the Copaxone into a vein or an artery. The case specified that a patient was involved; however no other details were provided in the case narrative.

These cases did not provide sufficient details that would indicate the root cause for these accidental injections. Therefore, no changes to the label are recommended based on these cases.

Wrong Schedule (n=2)³

The first case (ISR 7812861) describes a patient who was taking Copaxone 20 mg every other day; however, it was unclear if those were the prescribed directions. The patient was pregnant during therapy and experienced several medical events during the pregnancy and delivery (including seizure, tachycardia, difficulty breathing, and fever), it is unknown if any of the events were related to the medication. The child was declared healthy at birth and the patient discontinued

³ ISR numbers: 7812861, 8239914

the drug for one month after the delivery. Treatment with Copaxone resumed and no other relevant details were provided in the report.

The second case (ISR 8239914) describes a patient who experienced adverse reactions such as photosensitivity / rash upon sun exposure and palpitations. The report states that the frequency was reduced to every other day and that therapy continues. The patient also experienced injection site reactions which resolved with rotating the injection sites and warming the injection sites. No other relevant details or outcomes were provided.

The correct daily dosing schedule is clearly stated in the product information. No changes to the label are recommended based these cases.

2.2.4 FDA Name Simulation Studies

Thirty-six practitioners participated in DMEPA’s prescription studies. Most practitioners interpreted the name correctly as Glatopa (25 out of 36). The remaining misinterpretations did not overlap with or appear or sound similar to any currently marketed products. Common misinterpretation of the outpatient prescription was the letter ‘o’ for the letter ‘a’ at the end of the name (5 of 14). All other misinterpretations were also single letter errors which were expected (e.g. voice studies ‘b’ instead of ‘p’, and ‘i’ or ‘y’ instead of ‘a’). See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

2.2.5 Comments from Other Review Disciplines

In response to the OSE email on December 5, 2011, the Division of Neurology Products (DNP) and Office of Generic Drugs indicated that they had no objections to the proposed proprietary name, Glatopa.

2.2.6 Failure Mode and Effects Analysis of Similar Names

Appendix B lists possible orthographic and phonetic misinterpretations of the letters appearing in the proposed proprietary name, Glatopa. Table 1 lists the names with orthographic and phonetic similarity to the proposed proprietary name, Glatopa, identified by the primary reviewer, (b) (4) [company which performed the name study for the Applicant], and the Expert Panel Discussion (EPD), which required further evaluation.

Table 1: Collective List of Potentially Similar Names

Look Similar					
Name	Source	Name	Source	Name	Source
Gladese	EPD	Glucagen	EPD	Citalopram	(b) (4)
Claravis	EPD	Glucamide	EPD	Glipizide	(b) (4)
Clobex	EPD	Clolar	EPD	Insulin Glargine	(b) (4)
Clofarex	EPD	Glutofac	EPD	Keppra	(b) (4)

Clopra	EPD	Glutofac-ZX	EPD	Zolpidem	(b) (4)
Gilenya	EPD	Glutofac-MX	EPD	Gladyne	EPD
(b) (4)	EPD	Glucagon	EPD/ (b) (4)	Stelara	EPD
Claforan	EPD/ (b) (4)	Glucophage	EPD	Cloxacpen	EPD
Clobazam	EPD	Glumetza	EPD	Glucose	EPD
Cloderm	EPD	Jenloga	EPD		
Sound Similar					
Latuda	EPD	Methylidopa	(b) (4)	Parcopa	(b) (4)
Topamax	(b) (4)	Yutopar			
Sound and Look Similar					
Gabatopa	EPD	Levodopa/ Carbidopa	(b) (4)	Glucotrol	(b) (4) (EPD as Look similar)

Our analysis of the 37 names contained in Table 1 considered the information obtained in the previous sections along with their product characteristics. We determined that the 37 names will not pose a risk for confusion as described in Appendix D and E.

2.2.7 Communication of DMEPA's Final Decision to Other Disciplines

DMEPA communicated these findings to the Division of Office of Generic Drugs via e-mail on June 28, 2012. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the Division of Neurology Products on July 6, 2012, they stated no additional concerns with the proposed proprietary name, Glatopa.

2.3 SAFETY ASSESSMENT OF PROPOSED LABELS, LABELING AND PACKAGING

DMEPA identified the following with the proposed labels and labeling submitted on February 21, 2012:

- Missing lot and expiration date on the blister label.
- Confusing strength presentation on the blister label
- The proprietary name is expressed in all capital letters which decreases readability on all carton and container labels and labeling.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

DMEPA identified deficiencies with the proposed labels and labeling that require revision prior to approval. Our recommendations are provided in section 3.2 below.

If you have further questions or need clarifications, please contact Laurie Kelley, OSE project manager, at 301-796-5068.

3.1 DMEPA COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Glatopa, and have concluded that this name is acceptable. However, if any of the proposed product characteristics as stated in your November 3, 2011 submission are altered, the name must be resubmitted for review. Additionally, this proprietary name must be re-evaluated 90 days prior to the approval of the application. The conclusions upon re-review are subject to change.

3.2 DMEPA COMMENTS TO OGD FOR THE APPLICANT

A. All Labels and Labeling

1. Revise the presentation of the proprietary name from all capital letters to title case letters “Glatopa”. The established name should have a prominence commensurate with the prominence of the proprietary name including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

B. Blister Label

1. Ensure that the lot number and expiration date are presented on the label per 21 CFR 201.17 and 201.18.
2. Revise the strength presentation to read 20 mg/mL. Follow customary placement of the proprietary name, established name, and strength on the label, to read:

Glatopa
(glatiramer acetate injection)
20 mg/mL

REFERENCES

1. ***Micromedex Integrated Index*** (<http://csi.micromedex.com>)
Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.
2. ***Phonetic and Orthographic Computer Analysis (POCA)***
POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.
3. ***Drug Facts and Comparisons, online version, St. Louis, MO*** (<http://factsandcomparisons.com>)
Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products. This database also lists the orphan drugs.
4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***
DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.
5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***
This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.
6. ***Drugs@FDA*** (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)
Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.
7. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)
USPTO provides information regarding patent and trademarks.
8. ***Clinical Pharmacology Online*** (www.clinicalpharmacology-ip.com)
Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common,

combination, nutraceutical and nutritional products. It also provides a keyword search engine.

9. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

10. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

11. Access Medicine (www.accessmedicine.com)

Access Medicine® from McGraw-Hill contains full-text information from approximately 60 titles; it includes tables and references. Among the titles are: Harrison's Principles of Internal Medicine, Basic & Clinical Pharmacology, and Goodman and Gilman's The Pharmacologic Basis of Therapeutics.

12. USAN Stems (<http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml>)

USAN Stems List contains all the recognized USAN stems.

13. Red Book (www.thomsonhc.com/home/dispatch)

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

14. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

15. Medical Abbreviations (www.medilexicon.com)

Medical Abbreviations dictionary contains commonly used medical abbreviations and their definitions.

16. CVS/Pharmacy (www.CVS.com)

This database contains commonly used over the counter products not usually identified in other databases.

17. Walgreens (www.walgreens.com)

This database contains commonly used over the counter products not usually identified in other databases.

18. Rx List (www.rxlist.com)

RxList is an online medical resource dedicated to offering detailed and current pharmaceutical information on brand and generic drugs.

19. Dogpile (www.dogpile.com)

Dogpile is a [Metasearch](#) engine that searches multiple search engines including Google, Yahoo! and Bing, and returns the most relevant results to the search.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment considers the promotional and safety aspects of a proposed proprietary name. The promotional review of the proposed name is conducted by OPDP. OPDP evaluates proposed proprietary names to determine if they are overly fanciful, so as to misleadingly imply unique effectiveness or composition, as well as to assess whether they contribute to overstatement of product efficacy, minimization of risk, broadening of product indications, or making of unsubstantiated superiority claims. OPDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.

The safety assessment is conducted by DMEPA. DMEPA staff search a standard set of databases and information sources to identify names that are similar in pronunciation, spelling, and orthographically similar when scripted to the proposed proprietary name. Additionally, we consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.). DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.⁴

Following the preliminary screening of the proposed proprietary name, DMEPA gathers to discuss their professional opinions on the safety of the proposed proprietary name. This meeting is commonly referred to the Center for Drug Evaluation and Research (CDER) Expert Panel discussion. DMEPA also considers other aspects of the name that may be misleading from a safety perspective. DMEPA staff conducts a prescription simulation studies using FDA health care professionals. When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name

⁴ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

and misleading nature of the proposed proprietary name with a focus on the avoidance of medication errors.

DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product. DMEPA considers the product characteristics associated with the proposed product throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. DMEPA considers how these product characteristics may or may not be present in communicating a product name throughout the medication use system. Because drug name confusion can occur at any point in the medication use process, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁵

The DMEPA considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA compares the proposed proprietary name with the proprietary and established name of existing and proposed drug products and names currently under review at the FDA. DMEPA compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. DMEPA examines the phonetic similarity using patterns of speech. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice. The orthographic appearance of the proposed name is evaluated using a number of different handwriting samples. DMEPA applies expertise gained from root-cause analysis of postmarketing medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details).

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Table 1. Criteria Used to Identify Drug Names that Look- or Sound-Similar to a Proposed Proprietary Name.

Type of Similarity	Considerations when Searching the Databases		
	<i>Potential Causes of Drug Name Similarity</i>	<i>Attributes Examined to Identify Similar Drug Names</i>	<i>Potential Effects</i>
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name/Similar shape Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, DMEPA considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA

considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA searches the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name. A standard description of the databases used in the searches is provided in the reference section of this review. To complement the process, the DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel. DMEPA also evaluates if there are characteristics included in the composition that may render the name unacceptable from a safety perspective (abbreviation, dosing interval, etc.).

2. Expert Panel Discussion

DMEPA gathers CDER professional opinions on the safety of the proposed product and discussed the proposed proprietary name (Expert Panel Discussion). The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Office of Prescription Drug Promotion (OPDP). We also consider input from other review disciplines (OND, ONDQA/OBP). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the database and information searches to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend additional names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Simulation Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or

outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

4. Comments from Other Review Disciplines

DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, considers all aspects of the name that may be misleading or confusing, conducts a Failure Mode and Effects Analysis, and provides an overall decision on acceptability dependent on their risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the

⁶ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section 1.2 of this review. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

“Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting? And are there any components of the name that may function as a source of error beyond sound/look-alike?”

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity or because of some other component of the name. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

Moreover, DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Overall Risk Assessment:

- a. OPDP finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with OPDP’s findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product but involve a naming characteristic that when incorporated into a proprietary name, may be confusing, misleading, cause or contribute to medication errors.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA generally recommends that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Applicant/Sponsor. However, the safety concerns set forth in criteria a through e above are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names, confusing, or misleading names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the

past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval.

6. Safety Evaluator Risk Assessment of the Proposed Product and associated labels and labeling

DMEPA searches the FDA AERS database for any medication error reports associated with the reference listed drug that may be relevant to this product. We also evaluate labels and package insert labeling submitted by the Applicant using the principals of Human Factors and Failure Mode and Effects Analysis,⁷ along with post marketing medication error data.

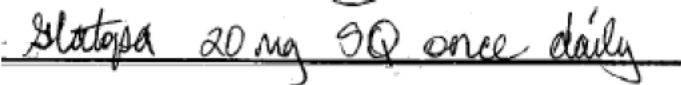
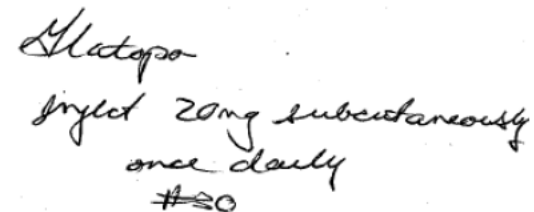
⁷ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Appendix B: Letters and Letter Strings with Possible Orthographic or Phonetic Misinterpretation

Letters in Name, Glatopa	Scripted may appear as	Spoken may be interpreted as
Upper case 'G'	'C'	'K', 'J'
Lower case 'g'	'q', 'j', 's'	'K', 'J'
Lower case 'l'	'b', 'e', 's', 'i'	'w'
Lower case 'a'	'o', 'e', 'u', 'el'	Any vowel
Lower case 't'	'l', 'r', 'f', 'x'	'D'
Lower case 'o'	'a', 'c', 'e', 'u'	'Oh'
Lower case 'p'	'ys'	'B'
Lower case 'a'	'o', 'e', 'u', 'el'	Any vowel

Appendix C: Prescription Simulation Samples and Results

Figure 1. Glatopa Study (Conducted on November 25, 2011)

Handwritten Requisition Medication Order	Verbal Prescription
<p><u>Medication Order:</u></p> 	<p>Glatopa</p> <p>Inject 20 mg subcutaneously once daily</p> <p>#30</p>
<p><u>Outpatient Prescription:</u></p> 	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

85 People Received Study
36 People Responded

Study Name: Glatopa

Total	12	10	14	36
INTERPRETATION	INPATIENT	VOICE	OUTPATIENT	TOTAL
GLADTOPA	0	1	0	1
GLATAPA	0	0	1	1
GLATOBA	0	1	0	1
GLATOPA	12	5	8	25
GLATOPO	0	0	5	5
GLITOPA	0	1	0	1
GLYTOPA	0	1	0	1
LATOPA	0	1	0	1

Appendix D: Proprietary names not likely to be confused or not used in usual practice settings for the reasons described.

Proprietary Name	Active Ingredient	Similarity to Glatopa	Failure preventions
Celexa	Citalopram	Look alike	The pair has sufficient orthographic differences.
Claravis	Isotretinoin	Look alike	The pair has sufficient orthographic differences.
Glucamide	Chlorpropamide	Look alike	The pair has sufficient orthographic differences.
Glucotrol	Glipizide	Look alike for proprietary name	The pair has sufficient orthographic differences.
		Sound and Look alike for established name	The pair has sufficient orthographic and phonetic differences.
Clobex	Clobetasol propionate	Look alike	The pair has sufficient orthographic differences.
Clolar	Clofarabine	Look alike	The pair has sufficient orthographic differences.
Lantus	Insulin Glargine	Look alike	The pair has sufficient orthographic differences.
Clofarex	Clofarabine	Look alike	The pair has sufficient orthographic differences. The approved proprietary name for Clofarabine is Clolar. Access Medicine lists Clofarex as a related term.
Keppra	Levetiracetam	Look alike	The pair has sufficient orthographic differences.
Ambien	Zolpidem	Look alike	The pair has sufficient orthographic differences.
Clopra	Metoclopramide	Look alike	The pair has sufficient orthographic differences.
Gladyne	Iris pallida – herbal supplement	Look alike	Unable to find product characteristics in commonly used drug databases

Proprietary Name	Active Ingredient	Similarity to Glatopa	Failure preventions
(b) (4)***	Dexlansoprazole	Look alike	Identified in previously proposed names database. Established name for NDA 022287 is approved and marketed under different proprietary name, Dexilant.
Claforan	Cefotaxime	Look alike	The pair has sufficient orthographic differences.
Glucophage	Metformin	Look alike	The pair has sufficient orthographic differences.
Stelara	Ustekinumab	Look alike	The pair has sufficient orthographic differences.
Glumetza	Metformin	Look alike	The pair has sufficient orthographic differences.
Cloderm	Clocortolone Pivalate	Look alike	The pair has sufficient orthographic differences.
Topamax	Topiramate	Sound alike	The pair has sufficient phonetic differences.
Latuda	Lurasidone	Sound alike	The pair has sufficient phonetic differences.
Aldomet	Methyldopa	Sound alike	The pair has sufficient phonetic differences.
Yutopar	Ritodrine	Sound alike	The pair has sufficient phonetic differences.
Parcopa	Carbidopa / Levodopa	Sound alike for proprietary name	The pair has sufficient phonetic differences.
		Look and Sound alike for established name	The pair has sufficient orthographic and phonetic differences
Gabatopa	Topiramate	Look and Sound alike	The pair has sufficient orthographic and phonetic differences. Foreign product name only available in South Korea. Available as Topamax in US.

Appendix E: Risk of medication errors due to product confusion minimized by dissimilarity of the names and/ or use in clinical practice for the reasons described.

<p>Proposed name: Glatopa</p> <p>Dosage Form(s): Solution for injection (prefilled syringe)</p> <p>Strength(s): 20 mg/mL</p> <p>Usual Dose and Frequency and Route: 20 mg daily subcutaneous injection</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p><u>Glucagen (Glucagon</u> <u>Hydrochloride)</u></p> <p><u>Strength and Dosage</u> <u>Form:</u> 1 mg / mL vial</p> <p><u>Dose, Route and</u> <u>Frequency:</u> 1 mL or 0.5 mL subcutaneously, intramuscularly or intravenously once then repeat if necessary</p> <p>As a diagnostic agent the dose is from 0.2 mg to 2 mg, given intravenously or intramuscularly as a one time injection.</p>	<p>Orthographic similarity to both the established and proprietary names</p> <p>When scripted the prefix Glu- looks like the prefix Gla-. The upstroke ‘l’ and downstrokes ‘g’ and ‘p’ are in the same positions for all names.</p> <p>Overlapping product characteristics</p> <p>Same route of administration (subcutaneous), same dose (1 mL), both products are single strength.</p>	<p>Orthographic differences</p> <p>Glatopa has an additional upstroke/cross stroke ‘t’ as compared to Glucagen and Glucagon, giving the names different shapes when scripted.</p> <p>Key differences in product characteristics</p> <p><u>Frequency:</u> Glatopa is administered on a scheduled basis daily vs. Glucagen which is typically administered once on an as needed basis.</p>

<p>Proposed name: Glatopa</p> <p>Dosage Form(s): Solution for injection (prefilled syringe)</p> <p>Strength(s): 20 mg/mL</p> <p>Usual Dose and Frequency and Route: 20 mg daily subcutaneous injection</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Gilenya (fingolimod)</p> <p><u>Strength and Dosage</u> <u>Form:</u> 0.5 mg capsule</p> <p><u>Dose, Route and</u> <u>Frequency:</u> 0.5 mg or 1 capsule by mouth once daily</p>	<p>Orthographic similarity</p> <p>When scripted the The upstroke ‘l’ and downstrokes ‘y’ and ‘p’ are in similar positions for each name. Both names start with the letter ‘G’ and have 7 letters in each name.</p> <p>Overlapping product characteristics</p> <p>Same frequency, both products are single strength which may be omitted.</p>	<p>Orthographic differences</p> <p>Glatopa has an additional upstroke/cross stroke ‘t’ as compared to Gilenya, giving the names different shapes when scripted.</p>

<p>Proposed name: Glatopa</p> <p>Dosage Form(s): Solution for injection (prefilled syringe)</p> <p>Strength(s): 20 mg/mL</p> <p>Usual Dose and Frequency and Route: 20 mg daily subcutaneous injection</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Clobazam (established name for Onfi)</p> <p><u>Strength and Dosage Form:</u> 5 mg, 10 mg, and 20 mg tablets</p> <p><u>Dose, Route and Frequency:</u> 5 mg to 40 mg per day, orally, once (5 mg) or twice daily (doses above 5 mg)</p>	<p>Orthographic similarity</p> <p>When scripted The prefix Clo- looks similar to the prefix Gla-. When the ‘z’ in clobazam is written with a downstroke, both names have the same number of up and down strokes in the same positions.</p> <p>Overlapping product characteristics</p> <p>Overlapping dose, strength (20 mg) and frequency.</p>	<p>Orthographic differences</p> <p>Glatopa has an cross stroke ‘t’ vs. a ‘b’ in Clobazam.</p> <p>The suffix -zam in Clobazam appears sufficiently different from the suffix -pa in Glatopa, when scripted.</p>

<p>Proposed name: Glatopa</p> <p>Dosage Form(s): Solution for injection (prefilled syringe)</p> <p>Strength(s): 20 mg/mL</p> <p>Usual Dose and Frequency and Route: 20 mg daily subcutaneous injection</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Cloxapen (Cloxacillin)</p> <p><u>Strength and Dosage Form:</u> 250 mg and 500 mg capsules</p> <p><u>Dose, Route and Frequency:</u> 250 mg to 500 mg orally every 6 hours</p>	<p>Orthographic similarity</p> <p>When scripted The prefix Clo- looks similar to the prefix Gla-. The upstrokes ‘l’ and downstrokes ‘p’ are in the same positions for each name.</p>	<p>Key differences in product characteristics</p> <p><u>Strength:</u> Cloxapen is available in two strengths which must be written on a prescription vs. the single strength of Glatopa. There is no overlap in strength.</p>

<p>Proposed name: Glatopa</p> <p>Dosage Form(s): Solution for injection (prefilled syringe)</p> <p>Strength(s): 20 mg/mL</p> <p>Usual Dose and Frequency and Route: 20 mg daily subcutaneous injection</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Jenloga (Clonidine)</p> <p><u>Strength and Dosage Form:</u> 0.1 mg and 0.2 mg extended release tablet</p> <p><u>Dose, Route and Frequency:</u> 0.1 mg to 0.4 mg per day, orally once daily (0.1 mg only) or twice daily</p>	<p>Orthographic similarity</p> <p>Both names have the same number of letters (n=7).</p> <p>The two downstrokes ‘j’ (lower case) and ‘g’ and one upstroke ‘l’ in Jenloga are in the same positions as the two downstrokes ‘g’ and ‘p’ and upstroke ‘t’ in Glatopa.</p> <p>Overlapping product characteristics</p> <p>Overlapping frequency of administration (once daily)</p>	<p>Orthographic differences</p> <p>Glatopa has a cross stroke ‘t’ vs. the ‘l’ in Jenloga. Glatopa also has an additional upstroke ‘l’ in the second position, giving the names different shapes when scripted.</p> <p>Key differences in product characteristics</p> <p><u>Strength:</u> Jenloga is available in two strengths which must be written on a prescription vs. the single strength of Glatopa. There is no overlap in strength.</p>

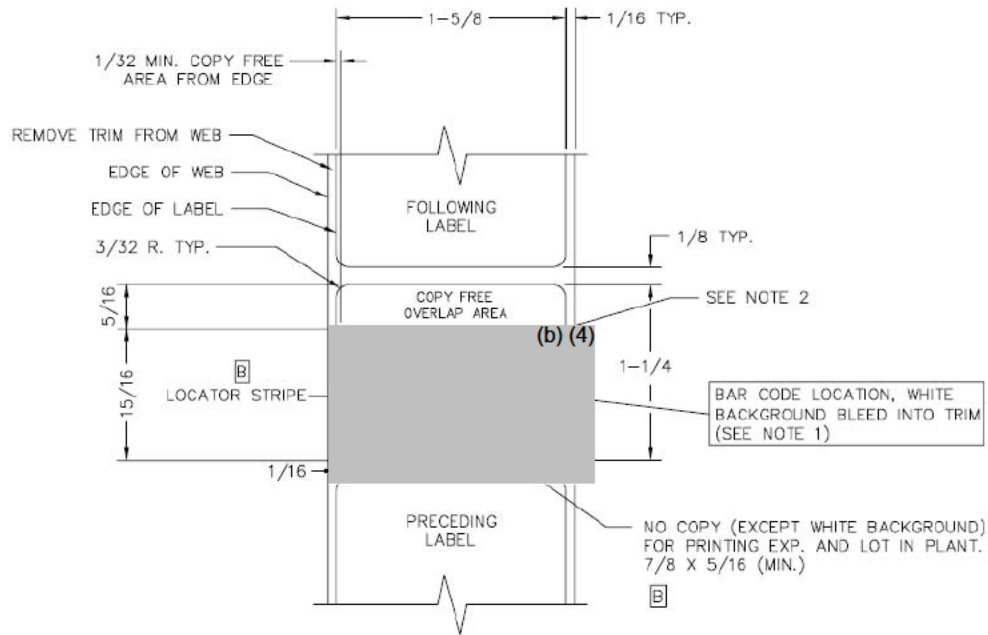
<p>Proposed name: Glatopa</p> <p>Dosage Form(s): Solution for injection (prefilled syringe)</p> <p>Strength(s): 20 mg/mL</p> <p>Usual Dose and Frequency and Route: 20 mg daily subcutaneous injection</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Glucose (Dextrose)</p> <p><u>Strength and Dosage</u> <u>Form:</u> 5 gm chewable tablet and 40 % oral gel</p> <p><u>Dose, Route and</u> <u>Frequency:</u> 1 tablet or contents of 1 tube orally once, may be repeated</p>	<p>Orthographic similarity</p> <p>Both names start with the same letter ‘G’ and have the same number of letters. When scripted the prefix Glu- looks like the prefix Gla-. Both names have a cross stroke ‘t’ in the same positions.</p> <p>Overlapping product characteristics</p> <p>Similarity in dose 1 tab / tube vs. 1 mL</p>	<p>Orthographic differences</p> <p>Glatopa has an additional downstroke ‘p’ vs. Glucose, which does not.</p> <p>Key differences in product characteristics</p> <p><u>Frequency:</u> Glatopa is administered on a scheduled basis daily vs. Glucose which is typically administered once on an as needed basis.</p>

<p>Proposed name: Glatopa</p> <p>Dosage Form(s): Solution for injection (prefilled syringe)</p> <p>Strength(s): 20 mg/mL</p> <p>Usual Dose and Frequency and Route: 20 mg daily subcutaneous injection</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Gladase (Papain / Urea)</p> <p><u>Strength and Dosage Form:</u> 110000-10%, 1100000-10%, 650000-10%, 830000- 10%, 830000-100 mg topical ointment</p> <p><u>Dose, Route and Frequency:</u> Apply sufficient amount topically, frequency unknown</p>	<p>Orthographic similarity</p> <p>Both names start with the same letter ‘G’ and have the same number of letters. The prefixes Gla- are the same in both names. Both names have an additional upstroke in the same position ‘t’ vs. ‘d’ .</p>	<p>Orthographic differences</p> <p>Glatopa has a cross stroke ‘t’ vs. the ‘d’ in Gladase and Glatopa has an additional down stroke ‘p’ giving the names different shapes when scripted.</p> <p>Key differences in product characteristics</p> <p><u>Strength:</u> Gladase is available in multiple strengths which must be written on a prescription vs. the single strength of Glatopa. There is no overlap in strength.</p>

<p>Proposed name: Glatopa</p> <p>Dosage Form(s): Solution for injection (prefilled syringe)</p> <p>Strength(s): 20 mg/mL</p> <p>Usual Dose and Frequency and Route: 20 mg daily subcutaneous injection</p>	<p>Failure Mode: Incorrect Product Ordered/ Selected/Dispensed or Administered because of Name confusion</p> <p>Causes (could be multiple)</p>	<p>Prevention of Failure Mode</p> <p>In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names</p>
<p>Glutofac / Glutofac MX / Glutofac ZX (multivitamin with minerals)</p> <p><u>Strength and Dosage Form:</u> Each are single strength tablets</p> <p><u>Dose, Route and Frequency:</u> Information not available for these products, however typically for multivitamin solid oral dosage forms are taken as 1 tablet once daily on a scheduled basis.</p>	<p>Orthographic similarity</p> <p>Both names start with the same letter ‘G’. When scripted the prefixes Gla- and Glu appear similar same in both names. The names have cross stroke ‘t’ in the same positions. When the ‘f’ in Glutofac is written with a downstroke both names have a downstroke in the same positions.</p> <p>Overlapping product characteristics</p> <p>Overlapping frequency and all are single strength products.</p>	<p>Orthographic differences</p> <p>Both Glutofac ZX and MX contain modifiers, and if written they will distinguish each drug from Glatopa. Additionally, the suffix –fac in Glutofac appears sufficiently different from the suffix –pa in Glatopa when scripted.</p>

Appendix F: Appendix Syringe Label, Blister Label, and Carton Labeling Submitted
February 21, 2012

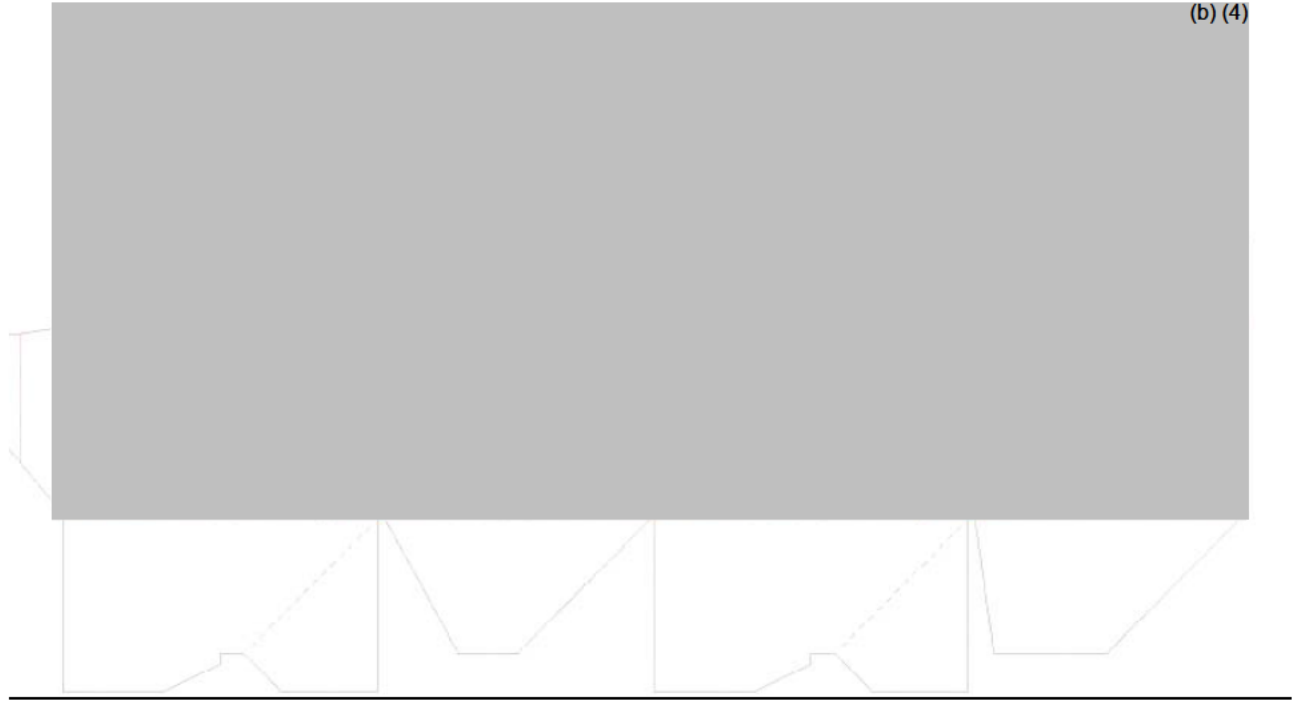
Syringe Label



Blister Label



Carton Labeling



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEKSANDER P WINIARSKI
01/17/2013

JAMIE C WILKINS PARKER
01/17/2013

CAROL A HOLQUIST
01/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 090218

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form		Author: Heather Strandberg

Approval Type: <input checked="" type="checkbox"/> FULL APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)		
RPM: KAM Team:		Approval Date:
<input type="checkbox"/> PI <input type="checkbox"/> PII <input checked="" type="checkbox"/> PIII <input type="checkbox"/> PIV (eligible for 180 day exclusivity) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> MOU <input checked="" type="checkbox"/> RX or <input type="checkbox"/> OTC		
ANDA #: 090218 Applicant: Sandoz, Inc. Established Product Name: Glatopa (Glatiramer Acetate) Injection 20 mg/mL Basis of Submission (RLD): 020622 (Is ANDA based on an approved Suitability Petition? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No)		
Does the ANDA contain REMS? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No (If YES, initiate approval action 6 weeks prior to target action date)		
Regulatory Project Manager Evaluation:		Date: 04/16/2015
<input checked="" type="checkbox"/> Date last Complete Response (CR) letter was issued -- Date August 19, 2014 <input type="checkbox"/> Previously reviewed and tentatively approved (if applicable) --- Date _____		
Date of Application December 26, 2007		Original Rec. Date December 27, 2007 Acceptable for Filing December 27, 2007
YES	NO	
<input type="checkbox"/>	<input type="checkbox"/>	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)
		Date of Acceptable Quality April 15, 2015 Date of Acceptable Dissolution N/A Date of Acceptable Bioequivalence October 21, 2013 Date of Acceptable Labeling April 14, 2014
		If applicable: Date of Acceptable Microbiology March 31, 2014 Date of Acceptable Clinical Review July 7, 2014 Date of Acceptable REMS N/A
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Are consults pending for any discipline?
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES → Verify a second filing review was completed and that all disciplines completed new reviews <input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Is there a pending Citizen Petition (CP)?
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Overall OC Recommendation is acceptable (EES is acceptable) Date Acceptable: _____ Re-evaluation Date: August 16, 2015
<input checked="" type="checkbox"/>	<input type="checkbox"/>	OSI Clinical Endpoint and Bioequivalence Site Inspections are acceptable
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff (OGDREQUEST) 30 to 60 days prior to approval, Date emailed OGD Aware
Draft Approval/Tentative Approval Letter		
<input type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter is drafted and uploaded to the Final Decision task
Review Discipline/Division Endorsements		

Lead Division: Program Management Effective Date: 10/1/2014 Page 1 of 10

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

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Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

<input checked="" type="checkbox"/>	<input type="checkbox"/>	Division of Legal and Regulatory Support Endorsement completed, Date 12/01/2014
<input type="checkbox"/>	<input checked="" type="checkbox"/>	Paragraph IV Evaluation completed (if applicable), Date N/A
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Quality Endorsement completed, Date 04/15/2015
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Bioequivalence Endorsement completed, Date 04/15/2015
<input checked="" type="checkbox"/>	<input type="checkbox"/>	Labeling Endorsement completed, Date 04/10/2015
<input type="checkbox"/>	<input checked="" type="checkbox"/>	REMS Endorsement (if applicable), Date N/A
<u>RPM Team Leader Endorsement and Action Package Verification</u>		
<input checked="" type="checkbox"/>	<input type="checkbox"/>	RPM Team Leader Endorsement completed, Date 04/15/2015
<u>Final Decision and Letter Sign-off</u>		
<input type="checkbox"/>	<input type="checkbox"/>	Final Decision recommending approval/tentative approval completed, Date _____
<input type="checkbox"/>	<input type="checkbox"/>	Approval/Tentative Approval letter electronically signed, Date: _____
<u>Project Close-Out</u>		
<input type="checkbox"/>	<input type="checkbox"/>	Notify applicant of approval and provide a courtesy copy of the electronically signed letter
<input type="checkbox"/>	<input type="checkbox"/>	Is there a Post Marketing Agreement (PMA)? IF YES → Send email to PMA coordinator, Date emailed _____
<input type="checkbox"/>	<input type="checkbox"/>	Email OGD Approval distribution list (CDER-OGDAPPROVALS) with approval information

This page to be completed by the RPM

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 12/1/2014
Name/Title: MHS

Contains GDEA certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Pediatric Exclusivity System RLD = _____ NDA# _____ Date Checked _____ Nothing Submitted <input type="checkbox"/> Written request issued <input type="checkbox"/> Study Submitted <input type="checkbox"/>
(required if sub after 6/1/92)	
Patent/Exclusivity Certification: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	
If Para. IV Certification- did applicant:	
Notify patent holder/NDA holder Yes <input type="checkbox"/> No <input type="checkbox"/>	
Was applicant sued w/in 45 days: Yes <input type="checkbox"/> No <input type="checkbox"/>	
Has case been settled: Yes <input type="checkbox"/> No <input type="checkbox"/>	
Date settled:	
Is applicant eligible for 180 day	
Is a forfeiture memo needed: Yes <input type="checkbox"/> No <input type="checkbox"/>	

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Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

If yes, has it been completed	
Generic Drugs Exclusivity for each strength: Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Date of latest Labeling Review/Approval Summary	
Any filing status changes requiring addition Labeling Review Yes <input type="checkbox"/> No <input checked="" type="checkbox"/>	
Type of Letter:	
<input checked="" type="checkbox"/> APPROVAL <input type="checkbox"/> TENTATIVE APPROVAL <input type="checkbox"/> SUPPLEMENTAL APPROVAL (NEW STRENGTH)	
<input type="checkbox"/> OTHER:	

Comments:

ANDA submitted on 12/27/2007, BOS=Copaxone NDA 20622, PIV certs to '589, '430, '476, '161, '847, '539 and '098 patents(all patents exp. 5/24/2014). ANDA ack for filing with a PIV certification on 12/27/2007(LO dated 7/9/2008).

Between July 2008(issuance of the PIV ACK letter) and now Sandoz submitted multiple patent amendments to this ANDA. None of the information contained in these amendments is being memorialized on this ARS as at present time all patents listed for Copaxone 20 mg/mL have expired. It is noted that Sandoz was the first ANDA to be submitted containing a PIV to a listed patent and was once eligible for 180 day exclusivity. However, with the expiration of the 7 patents noted above, Sandoz no longer is eligible for 180 day exclusivity.

ANDA is eligible for immediate Full Approval but is no longer eligible for 180 day exclusivity.



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

2. *Paragraph IV Evaluation (for ANDAs with PIV certifications or other controversial regulatory issues)*

Date: _____ Name/Title: _____ Comments:

Or see corresponding endorsement task under the ANDA project within the platform

3. *Quality Endorsement by the Office of Pharmaceutical Science*

Date: _____ Name/Title: _____ Comments:

Or see corresponding endorsement task under the ANDA project within the platform

4. *Bioequivalence Endorsement*

Date: _____ Name/Title: _____ Comments:

Or see corresponding endorsement task under the ANDA project within the platform

5. *Labeling Endorsement*

Date: _____ Name/Title: _____ Comments:

Or see corresponding endorsement task under the ANDA project within the platform

6. *REMS Endorsement*

Date: _____ Name/Title: _____ Comments:



Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Or see corresponding endorsement task under the ANDA project within the platform

7. RPM Team Leader Endorsement

Date: _____ **Name/Title:** _____ **Comments:**

Or see corresponding endorsement task under the ANDA project within the platform

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Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 01
Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

8. Final Decision

Date: 4/16/2015

Name/Title: wpr

Para.IV Patent Cert: Yes No
Pending Legal Action: Yes No
Petition: Yes No
Entered to APTrack database
GDUFA User Fee Obligation Status Met Unmet
Press Release Acceptable
First Generic Approval
PD or Clinical for BE
Special Scientific or Reg. Issue

Date PETS checked for first generic drug _____

Comments:

BOS=Copaxone NDA 20622. The applicant provided PIV certs to '589, '430, '476, '161, '847, '539 and '098 patents. All of these patents expired on 5/24/2014 and are no longer a barrier to approval. Sandoz was the first ANDA submitted containing a PIV to a listed patent and was once eligible for 180 day exclusivity. Since all 7 patents noted above have expired, there is no longer a 180 day exclusivity. There is no exclusivity protecting the RLD. Chemistry acceptable 4/15/2015. QE 4/15/2015. Bio acceptable 4/15/2015 (waiver granted). Labeling acceptable 4/14/2014, TL sign-off 4/10/2015. EER acceptable till 8/16/2015. ANDA is eligible for immediate Full Approval.

Lead Division: Program Management	Effective Date: 10/1/2014	Page 6 of 10
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Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

EES DATA:

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Document Status: Approved		
Title: Approval Routing Summary Form	Author: Heather Strandberg	

Application History:

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4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

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MEMORANDUM

DATE: April 16, 2015

FROM: Robert A. Lionberger, Director
Office of Research and Standards, Office of Generic Drugs

Robert A. Lionberger -S

Digitally signed by Robert A. Lionberger -S
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ou=People, 0.9.2342.19200300.100.1.1=1300212309,
cn=Robert A. Lionberger -S
Date: 2015.04.16 08:14:37 -04'00'

THROUGH: Andre S. Raw, Acting Senior Scientific and Policy Adviser
Office of Lifecycle Drug Products, Office of Pharmaceutical Quality

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Sau L. Lee, Acting Associate Director for Science
Office of Pharmaceutical Quality

Sau L. Lee -S

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Date: 2015.04.16 09:08:58 -04'00'

TO: File for ANDA 90218

RE: Glatiramer Acetate Injection

I. SUMMARY

Several Abbreviated New Drug Applications (ANDAs) submitted for review to the Office of Generic Drugs (OGD) for glatiramer acetate injection reference New Drug Application (NDA) 20-622 for Copaxone (glatiramer acetate for injection), 20 milligrams (mg)/milliliter (mL) and 20 mg/vial sponsored by Teva Pharmaceuticals (Teva). Glatiramer acetate injection is a heterogeneous mixture of synthetic polypeptides synthesized from four naturally occurring amino acids – L-glutamic acid, L-alanine, L-tyrosine, and L-lysine. Copaxone is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

This memorandum describes (A) the history and other background information relating to multiple sclerosis and glatiramer acetate, (B) the structure, composition and chemical synthesis of glatiramer acetate, (C) active ingredient sameness criteria developed by OGD for glatiramer acetate injection, and (D) additional considerations undertaken in connection with establishing the foregoing criteria in response to arguments and data submitted in certain citizen petitions regarding Copaxone, including by Teva.¹

In a series of eight citizen petitions,² Teva requested that FDA refrain from approving any ANDA that references Copaxone as the reference listed drug (RLD) on numerous grounds, all of

¹ This memorandum reflects OGD's current thinking at the conclusion of a thorough review of issues relating to the general approvability of an ANDA for glatiramer acetate injection. As such, this memorandum supersedes other, previous OGD memoranda addressing these topics.

² Docket no. FDA-2008-P-0529, received on September 26, 2008, and responded to on March 25, 2009 (First Citizen Petition); docket no. FDA-2009-P-0555, received on November 13, 2009, and responded to on May 11,

which have been considered in developing our criteria for active ingredient sameness and other approval requirements. For the reasons described below, OGD has found Teva's assertions to be unpersuasive. Although the complexity of Copaxone is acknowledged and has been carefully considered, including as described in this memorandum, we have not found, as argued by Teva³ that this complexity alone would preclude a finding of active ingredient sameness between a generic glatiramer acetate injection and Copaxone. As described in greater detail below, OGD has found that an ANDA applicant for glatiramer acetate injection can demonstrate active ingredient sameness by showing equivalence between the ANDA product and the RLD as to the following four criteria:

1. Fundamental reaction scheme;
2. Physicochemical properties including composition;
3. Structural signatures for polymerization and depolymerization; and
4. Results in a biological assay.

As described in further detail below, the first three criteria provide successively refined evidence of active ingredient sameness, while the fourth criterion provides confirmation of active ingredient sameness established by the initial three criteria. As with all complex scientific issues, though, it is possible that with an improved understanding of the biological and clinical properties of glatiramer acetate and/or advances in the analytical technologies that might be used to characterize glatiramer acetate, other approaches might emerge to establish the active ingredient sameness of glatiramer acetate.

II. BACKGROUND

A. Glatiramer Acetate: Therapeutic Agent for Multiple Sclerosis

1. Multiple Sclerosis

Multiple sclerosis is a chronic inflammatory disease affecting the central nervous system (CNS) and causing lasting neurological impairment. It is a heterogeneous autoimmune disease

2010 (including the supplement thereto submitted on May 10, 2010, the Second Citizen Petition); docket no. FDA-2010-P-0642, received on December 10, 2010, and responded to on June 8, 2011 (including the supplement thereto submitted on February 22, 2011, Third Citizen Petition); docket no. FDA-2012-P-0555, received on June 4, 2012, and responded to on November 30, 2012 (Fourth Citizen Petition); docket no. FDA-2013-P-1128, received on September 12, 2013, and withdrawn by Teva on January 6, 2014; docket no. FDA-2013-P-1641, received on December 5, 2013 and responded to on May 2, 2014 (including the supplements thereto submitted on January 27, 2014, March 10, 2014, and May 2, 2014, the Sixth Citizen Petition); docket no. FDA-2014-P-0933, received on July 3, 2014 (including the supplements thereto submitted on July 17, 2014, August 12, 2014, and November 13, 2014, the Seventh Citizen Petition); and docket no. FDA-2015-P-1050, received on April 1, 2015 (the Eighth Citizen Petition).

³ See, e.g., Second Citizen Petition, at 2; Sixth Citizen Petition, at 26; Seventh Citizen Petition at 2, 8.

characterized by myelin degradation and concomitant axonal loss in the brain and spinal cord, but details of its pathogenesis are not well understood.⁴

Although the exact cause of multiple sclerosis is not known, multiple sclerosis is known to involve degradation of the myelin protein sheath (essentially an insulating layer) that surrounds and protects neurons.⁵ Through an unknown mechanism, myelin specific autoreactive T cells in the peripheral nervous system are able to cross the blood-brain barrier into the central nervous system. Upon entering the central nervous system, the autoreactive T cells interact with myelin degradation products such as myelin basic protein (MBP), myelin associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP).⁶ Such interactions stimulate inflammatory processes that activate B cells and autoaggressive T cells. Activated B cells release anti-myelin antibodies and stimulate the degradation of myelin peptides.⁷ Autoaggressive T cells release proinflammatory cytokines including TNF- α and IFN- γ which, in turn, activate macrophages. Activated macrophages can strip the myelin sheath and secrete molecules toxic to myelin such as matrix metalloproteinases, nitric oxide and free radicals.⁸ Together, these inflammatory processes cause disease progression that characterizes multiple sclerosis.

2. Discovery of Glatiramer Acetate and Approval of Copaxone

In 1971, a laboratory at the Weizmann Institute of Science initiated a study of amino acid copolymers designed to mimic MBP, one of the antigens postulated to cause multiple sclerosis and described above. The researchers expected to use their myelin mimics to initiate an immune response in animals and cause multiple sclerosis-like symptoms. Instead, they found that one of their copolymers inhibited the development of neurological symptoms in the animals under investigation.⁹ The study reported that a mixture of alanine, glutamic acid, tyrosine, and lysine formed a copolymer that inhibited experimental allergic encephalomyelitis (EAE), the primary

⁴ DeLuca GC, Williams K, Evangelou N, Ebers GC, Esiri MM. The contribution of demyelination to axonal loss in multiple sclerosis. *Brain* 2006; 129; 1507-1516.

⁵ Murphy K, Travers P, Walport M. *Janeway's Immunobiology*. 7th ed. New York: Garland Science; 2007; Dhib-Jalbut S, Arnold DL, Cleveland DW, et al. Neurodegeneration and neuroprotection in multiple sclerosis and other neurodegenerative diseases. *Journal of Neuroimmunology* 2006; 176; 198-215.

⁶ Ruggieri M, Avolio C, Livrea P, Trojano M. Glatiramer acetate in multiple sclerosis: a review. *CNS Drug Rev* 2007; 13:178-191.

⁷ Schrempf W, Ziemssen T. Glatiramer acetate: mechanisms of action in multiple sclerosis. *Autoimmun Rev* 2007; 6; 469-475.

⁸ Dhib-Jalbut S, Arnold DL, Cleveland DW, et al. Neurodegeneration and neuroprotection in multiple sclerosis and other neurodegenerative diseases. *Journal of Neuroimmunology* 2006; 176; 198-215.

⁹ Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of experimental allergic encephalomyelitis by a synthetic polypeptide. *European Journal of Immunology* 1971; 1; 242-248.

animal model for multiple sclerosis.¹⁰ The EAE inhibitor was dubbed “copolymer 1”¹¹ and was subsequently developed into the drug Copaxone. Glatiramer acetate is the active ingredient in Copaxone. In 1996, the FDA approved a New Drug Application submitted by Teva for Copaxone as a daily subcutaneous injection for the treatment of multiple sclerosis (NDA 20-622).

3. Mechanism of Action

Due to the heterogeneous nature of multiple sclerosis and the diverse population being treated, it has been postulated that an effective multiple sclerosis drug needs to invoke diverse immune system effects. Glatiramer acetate meets this need by providing a wide array of peptide copolymers that can activate the immune systems of many different individuals.¹² However, the mechanism of action of Copaxone remains, at least to some degree, unknown and incompletely characterized, despite several theories of mechanisms of action under investigation.

B. Composition and Synthesis

1. Peptide Copolymers

Glatiramer acetate is a mixture of peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate synthesis reaction are L-glutamic acid (Glu, E), L-lysine (Lys, K), L-alanine (Ala, A), and L-tyrosine (Tyr, Y) (see Figure 1), with an average molar fraction of 0.141, 0.338, 0.427, and 0.095 respectively.¹³ Glatiramer acetate has an average molecular weight of 5-9 kilodalton (kDa).¹⁴ The peptide copolymers in glatiramer acetate are synthesized via amino acid polymerization (followed by a subsequent cleavage or partial depolymerization step, each described further below). The resulting amino acid polymer chains vary in length and molecular weight.¹⁵

¹⁰ Lisak RP, Zweiman B, Blanchard N, Rorke LB. Effect of treatment with Copolymer 1 (Cop-1) on the in vivo and in vitro manifestations of experimental allergic encephalomyelitis (EAE). *Journal of Neurological Science* 1983; 62: 281-293.

¹¹ In the literature, glatiramer acetate is also referred to as Copaxone (Teva Neuroscience), Copolymer 1, Cop 1, COP, GA, Poly(Ala, Glu, Tyr, Lys), GLAT, and YEAK. In the last few years, multiple sclerosis researchers have standardized their nomenclature and now consistently use “glatiramer acetate” or “GA” to refer to the drug.

¹² Ruggieri M, Avolio C, Livrea P, Trojano M. Glatiramer acetate in multiple sclerosis: a review. *CNS Drug Reviews* 2007; 13: 178-91.

¹³ Current product labeling for NDA 020622 approved on January 28, 2014.

¹⁴ Id.

¹⁵ Varkony H, Weinstein V, Klinger E, Sterling J, Cooperman H, Komlos T, Ladkani D, Schwartz R. The glatiramoid class of immunomodulator drugs. *Expert Opinion Pharmacother.* 2009 10(4):657-668.

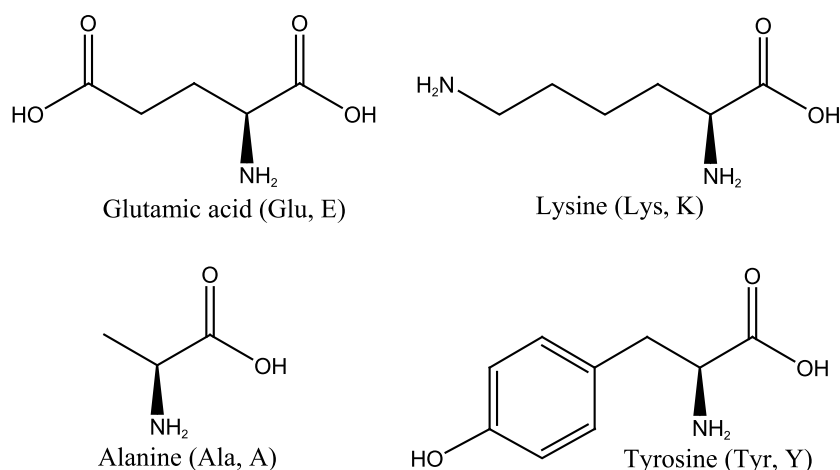
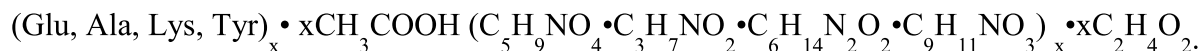


Figure 1. The four amino acids that make up glatiramer acetate.

Conserved Characteristics. The sequences of these four amino acids in each chain of the copolymer are neither entirely conserved (i.e., replicated) from batch to batch (as described further below) nor completely random.¹⁶ Rather, the sequences depend upon the physicochemical properties of the starting materials and upon the fundamental reaction chemistry used to manufacture glatiramer acetate, as well as upon the controls placed on various aspects of polymerization and depolymerization. The resultant drug product is, therefore, a mixture of peptide copolymers having an overall composition and physicochemical properties and, to the extent described below, amino acid sequences that are conserved, as described below, from batch to batch during its synthesis. The structural formula for glatiramer acetate is listed in the Copaxone labeling as:



Batch-to-Batch Variability. The chemical synthesis of Copaxone results in certain of its characteristics being conserved (e.g., its overall composition and physicochemical characteristics). The nature of Copaxone’s synthesis process, however, also results in a product with inherent variability, even when it is tightly controlled; there is a negligible likelihood that the specific amino acid sequences along the entire copolymer chain will be conserved from batch to batch. Rather, Copaxone exhibits batch-to-batch amino acid sequence variations across the copolymer, coupled with conservation of shorter “local” sequences within the copolymer.¹⁷

¹⁶ Copaxone has been described by Teva as having “a huge, perhaps incalculable number of active amino acid sequences” (First Citizen Petition at 6-7). We note, and have considered, the foregoing and other assertions made by Teva in its Citizen Petitions relating to the complexity of Copaxone and the large number of distinct amino acid chains comprising Copaxone (e.g., First Citizen Petition at 6-7, Second Citizen Petition at 2-3; 10; 21; Third Citizen Petition at 2, 14, 16; Fourth Citizen Petition at 10; Sixth Citizen Petition at 7 and the Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 4). However, as described here and elsewhere in this memorandum, this complexity does not preclude a finding of active ingredient sameness and ANDA approval.

¹⁷ We have observed this degree of batch-to-batch variability based on analyses of multiple batches of Copaxone conducted and submitted in connection with ANDAs as well as from FDA’s own internal laboratory analyses of

Therefore, both the conservation of certain characteristics from batch to batch of Copaxone (including Copaxone's local sequences, overall composition, and other physicochemical properties that are described in greater detail below), as well as the variations of other characteristics (including such longer amino acid sequences) between batches of Copaxone are fundamental properties of Copaxone. These conservation and variations characteristics have been considered in establishing active ingredient sameness criteria for a generic glatiramer acetate.

Copolymer, Rather Than a Protein. Glatiramer acetate is a copolymer composed of amino acids joined by peptide bonds. Although proteins are also composed of amino acids joined by peptide bonds, glatiramer acetate is distinguishable from proteins^{18, 19} because (unlike a protein)²⁰ it does not, as described above, have a defined and specific amino acid sequence.²¹ Rather, as noted above, in the glatiramer acetate mixture, there is a negligible likelihood of having identical amino acid sequences along entire copolymer chains from batch to batch. Conserved sequences in glatiramer acetate are instead limited to short amino acid sequences within the copolymer chain. Although these preserved local sequences may be reflected in analyses used to establish active ingredient sameness, there is also broader sequence variability inherent to Copaxone. As such, glatiramer acetate is best described not as a protein, but rather as a heterogeneous mixture of copolymers.

samples of Copaxone. We note that even for characteristics that are described in this response as “conserved” from batch to batch, we have observed some degree of batch-to-batch variability in Copaxone in terms of their levels and the use of the term “conserved” in this response in connection with such sequences intended to include this degree of variability. As described in this memorandum, both these variations and conserved aspects have been considered in establishing active ingredient sameness criteria for a generic glatiramer acetate, including through the use of equivalence ranges based on RLD variability.

¹⁸ Several of Teva's assertions in its Citizen Petitions relate to Copaxone having a complex and “protein-like” structure, which (as asserted by Teva) would preclude an active ingredient sameness determination of a generic glatiramer acetate (e.g., Second Citizen Petition at 2-3, 10, 13, 19; Third Citizen Petition at 3, 7-8; Fourth Citizen Petition at 1; Sixth Citizen Petition at 1-2, 3, 40 and Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 3-4, 5). However, as noted in this section and throughout this memorandum, OGD disagrees with this characterization.

¹⁹ We also note that several of Teva's assertions in its Citizen Petitions seem to indicate that although regulated as a drug product, Copaxone is in many ways more like, or shares characteristics with, a biological product (e.g., Fourth Citizen Petition, 33, 34; Sixth Citizen Petition at 36, 37, 40-41). Copaxone is a listed drug approved under section 505(c) of the Federal Food, Drug, and Cosmetic Act, and, thus, the ANDA approval pathway is available for generic glatiramer acetate injection.

²⁰ Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Feb. 2012), at 22.

²¹ Draft Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (Feb. 2012), at 13.

2. Synthesis

A fundamental reaction scheme for the manufacture of glatiramer acetate has been published.²² Additionally, patents describing the glatiramer acetate active ingredient (including its synthesis) have been published and, in some cases, listed in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).²³ These patents describe a fundamental reaction scheme that yields the glatiramer acetate active ingredient.

The fundamental reaction scheme for the synthesis of glatiramer acetate that is described in published literature can be subdivided into two critical steps:

²² Teitelbaum D, Meshorer A, Hirshfeld T, Arnon R, Sela M. Suppression of Experimental Allergic Encephalomyelitis by a Synthetic Polypeptide. *European Journal of Immunology*, 1971 (1) 242-248 describes the synthesis of glatiramer acetate as follows:

“Cop 1 (glatiramer acetate) was prepared from N-carboxyanhydrides of tyrosine, alanine, γ -benzyl glutamate, and ϵ , N-trifluoroacetyllysine. The polymerization reaction was carried out at room temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ -carboxyl groups of the glutamic acid was carried out with hydrogen bromide in glacial acetic acid and was followed by the removal of trifluoroacetyl groups from the lysine residues by 1M piperidine.”

²³ US Patent 7,199,098, previously listed in the Orange Book by Teva, describes the synthesis of copolymer -1 (glatiramer acetate) as follows:

“Protected copolymer-1 is prepared as described by Teitelbaum et al. Eur. J. Immun. Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 [grams (g)], alanine (50 g), τ -benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01-0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight $7,000 \pm 2,000$ Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20-28 °C a test reaction is performed on every batch at different time periods for example, from 10 -50 hours.

The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular-weight $7,000 \pm 2,000$ Da is calculated from the curve and performed on larger scale reaction. On average, working at 26 °C the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10 - 20 °C against water until a pH=8 is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5-6.0 is obtained. This solution is then concentrated and lyophilized to dryness.”

See also US Patent 6,048,898.

1. Polymerization (including initiation and propagation of polymerization) of the activated²⁴ amino acids (NCA-amino acids) alanine, tyrosine, glutamic acid, and lysine, which yields a copolymer comprised of alanine, tyrosine, glutamic acid, and lysine (and which is referenced throughout this memorandum as the intermediate copolymer),²⁵ and
2. Partial depolymerization of the intermediate copolymer to yield glatiramer acetate.

Although the patents and the published literature describe other steps (e.g., deprotection, filtration, and lyophilization) involved in the manufacturing process of glatiramer acetate, OGD determined from its analysis of publicly available synthesis-related information²⁶ that the conserved local amino acid sequences are primarily determined by the two critical steps of polymerization and partial depolymerization listed above and further described below. Therefore, the details of these two critical steps together with their characteristic properties and with the additional properties of glatiramer acetate injection (e.g., physicochemical properties) that are affected by all manufacturing steps, are also discussed in connection with the sameness criteria below.

Initiation of Polymerization. The first step of glatiramer acetate synthesis involves initiating the polymerization of NCA-amino acids. In a method described in the literature and in the patents,²⁷ the polymerization of the NCA-amino acids begins following addition of an initiator. The initiator reacts with an NCA-amino acid (tyrosine, glutamic acid, alanine, or lysine) to generate an initiator adduct (i.e., an amino acid bound to the initiator) (see Figure 2).²⁸ The initiation step

²⁴ Generally speaking, amino acids do not spontaneously polymerize. Activated or NCA- amino acids (e.g. *N*-carboxyanhydride amino acids) are chemically modified so that they can spontaneously polymerize into a polymer or copolymer following the addition of an initiator. The polymerization of NCA-amino acids to yield copolymers has been well studied and described in the literature (Katchalski E and Sela M. *Advances in Protein Chemistry* 1958; 13: 243). Based upon these studies, the polymerization of the NCA-amino acids alanine, tyrosine, glutamic acid, and lysine used in first step of the synthesis of glatiramer acetate involve two fundamental steps: (a) initiation of polymerization; and (b) propagation of polymerization.

²⁵ These amino acids, particularly glutamic acid and lysine, may have attached protected side chains (e.g. the γ -O-benzyl ester for glutamic acid and ϵ -trifluoroacetic acid amide for lysine), which are removed during a deprotection step. As indicated by the Teitelbaum article and U.S. Patent 7,199,098, previously listed in the Orange Book, two of the amino acids used in the preparation of glatiramer acetate have protected side chains (γ -O-benzyl ester for glutamic acid and ϵ -trifluoroacetic acid amide for lysine) in order to avoid side reactions during polymerization. Therefore, following the polymerization and depolymerization reactions used to manufacture glatiramer acetate, a deprotection step may be needed to remove protecting groups on the lysine amino acid residues (e.g. the HBr depolymerization reaction yields trifluoroacetyl-copolymer-1 which is deprotected to yield copolymer-1 or glatiramer acetate). This deprotection step does not rearrange the order of amino acids in glatiramer acetate and therefore does not impact the molecular diversity of amino acid sequences in glatiramer acetate and, thus, is not considered a critical step in the overall reaction scheme.

²⁶ See note 23.

²⁷ See notes 22 and 23.

²⁸ The initiation reaction described in this memorandum is based upon the data evaluated by the Agency.

forms the C-terminus²⁹ of what will become a growing copolymer chain. Because of the intrinsic properties of the NCA-amino acids (e.g., relative bulkiness), the relative reactivity of each activated amino acid with initiator is anticipated to differ from the others. Most notably, the distribution of the four different initiator adducts at the C-terminus of the intermediate copolymer arises primarily because of the initiation kinetics and is a reflection of the reaction rate³⁰ of each of the NCA-amino acids and the initiator.

The amount of initiator used relative to the NCA-amino acids impacts the number of chains polymerized in a given polymerization reaction, which in turn impacts several characteristics of glatiramer acetate described below, including the length of the intermediate copolymer chains (which has a subsequent impact on local sequences in the chains) and the number of cleavages needed in the partial depolymerization.³¹ Each of these characteristics is incorporated into the active ingredient sameness criteria described below.

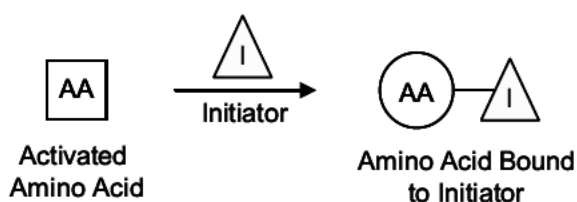


Figure 2. Polymerization of NCA-amino acids (abbreviated AA) begins with the addition of an initiator (abbreviated I).

Propagation of Polymerization. Following the initiation of polymerization, the amino acid of the growing polymer chain reacts with another NCA-amino acid to generate a copolymer comprised of two amino acids. This copolymer in turn, can react with another NCA-amino acid to generate a copolymer comprised of three amino acids. These copolymers will continue to react with remaining NCA-amino acids in a chain reaction and will yield a distribution of peptides composed of varying molecular weights and having varying sequences of alanine, tyrosine, glutamic acid, and lysine residues (see Figure 3). This sequential addition of amino acids that leads to a growing copolymer chain is termed polymer chain propagation. This process will continue until the NCA amino acids in the reaction solution are consumed.

²⁹ The C-terminus is the end of the copolymer chain in which the carboxylate group (or derivative thereof) is not linked to another amino acid. The N-terminus is the end of the copolymer chain in which the amine group is not linked to another amino acid.

³⁰ We note that the overall reaction rate is influenced both by each individual NCA-amino acid's intrinsic reactivity with the initiator, as well as (as described in greater detail below) the concentrations of the NCA-amino acids and initiator.

³¹ See, e.g., Shalitin Y. (1969), N-carboxy- carboxy- α -amino acid anhydrides, In Frisch K. and Reegen S. (Eds) Ring-opening Polymerization (pp. 421-496), New York and London: Marcel Dekker. See also, Zelzer M and Heise A, Determination of copolymerization characteristics in the N-carboxy anhydride polymerization of two amino acids, *Polymer Chemistry* 2013; 4: 3896.

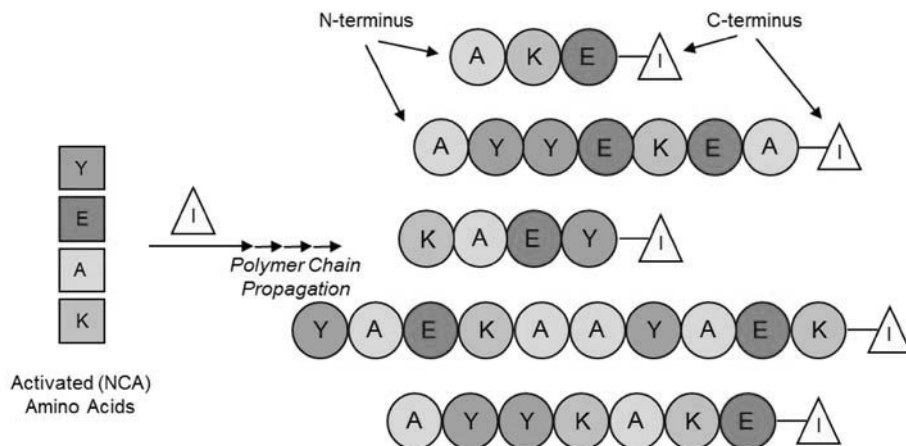


Figure 3. Depiction of the polymerization reaction used in the manufacture of glatiramer acetate to yield the intermediate copolymer. The addition of amino acids to the copolymer chain is known as polymer chain propagation. The abbreviations used are as follows: Y-tyrosine, E-glutamic acid, A-alanine, K-lysine.

We note that as the copolymer chain grows, while the addition of NCA-amino acids to the copolymer chain is not determined by a pre-determined sequence, it is also not a purely random event. Rather, each addition depends, in part, on the specific reaction kinetics at a given instant in the reaction, including, for example, the intrinsic reactivity of the NCA-amino acid added to the growing chain relative to the others, which is influenced by the size and shape of each NCA-amino acid. For instance, NCA-alanine is the smallest, most compact amino acid present in glatiramer acetate (Figure 1), allowing it to react more quickly than larger or more bulky amino acids (such as NCA-tyrosine). Based solely upon the bulk of the amino acids, one would expect the relative intrinsic reactivities of amino acids to differ and this would impact their relative incorporation rate into the copolymer during chain propagation in the following order: NCA-alanine > NCA-lysine ~ NCA-glutamic acid > NCA-tyrosine.^{32, 33}

The reaction kinetics (and therefore the rates of addition of the four NCA-amino acids), however, are not only dictated by their relative intrinsic reactivities, but also by the relative concentrations of the NCA-amino acids.³⁴ This is notable, because during polymerization, the relative

³² We note that, the intrinsic reactivities of polymerization reaction also depend on the specific amino acid residue including its derivatives (e.g. an amino acid residue with protecting group) in the copolymer, at which the propagation of a chain occurs. Nonetheless, the relative rank order of the four NCA-amino acids incorporated into the copolymer remains similar to the somewhat simplified discussion above and remains illustrative for purposes of the following discussion.

³³ We note that these relative reactivities were confirmed in connection with review of data submitted in Sandoz's ANDA.

³⁴ For example, the frequency with which an NCA-amino acid with a low intrinsic reactivity is added to a growing chain could be increased if its concentration relative to the other NCA-amino acids present in the polymerization reaction is also increased.

concentration of each of the four NCA-amino acids changes during the course of chain propagation. As the relative concentrations of NCA-amino acids are depleted or enriched during propagation, their corresponding relative rates of incorporation into the copolymer chains will change, leading to the process phenomenon of *propagational shift*.³⁵

Propagational Shift. The molar fraction of each of the four amino acids (i.e., tyrosine, glutamic acid, alanine, and lysine) in Copaxone is clearly defined.³⁶ If the four NCA-amino acids used in the synthesis had the same intrinsic reactivity during the chain propagation, the rates of incorporation of the four amino acids into the copolymer chains would be proportional to their respective molar fraction at the start of the reaction, which means that the molar fraction of each of the four NCA-amino acids in the polymerization solution would remain constant throughout the polymerization reaction. However, the intrinsic reactivities of the four NCA-amino acids involved are different, as described above, meaning that their corresponding relative rates of incorporation into the copolymer chains are, at any given point during the polymerization reaction, different from one another; these differing rates of incorporation result in shifting (rather than constant) molar fractions of each NCA-amino acid in the reaction solution, which in turn causes relative rates of incorporation of each NCA-amino acid into the copolymer to change throughout the propagation. As a result, the molar fractions of each of the four NCA-amino acids in the intermediate copolymer chain vary across the synthesized chain³⁷ (referred to throughout this memorandum as propagational shift).

To further illustrate propagational shift, during the initial phases of chain propagation, NCA-alanine, which is the most reactive NCA-amino acid and present at the highest concentration in the initial reaction solution (with a relative molar fraction in glatiramer acetate of 0.427), will be incorporated into the growing copolymer chain at the fastest rate. At the other extreme, during this period, NCA-tyrosine, which is the least reactive NCA-amino acid and present at the lowest concentration in the initial reaction solution (with a relative molar fraction in glatiramer acetate of 0.095), will be incorporated into the growing copolymer chain most slowly. Therefore, during the initial phases of chain propagation, the initial portion of the growing copolymer chain will be composed of relatively high levels of alanine with correspondingly low levels of tyrosine.

However, during the course of polymerization, as NCA-alanine is being rapidly incorporated into the growing polymer chains, its concentration relative to the other NCA-amino acids in the reaction solution will be reduced. As a result, toward the latter end of the chain propagation, the concentration of NCA-alanine will be reduced and its relative rate of incorporation into the polymer (or reactivity) will decrease. Therefore, during the later phases of chain propagation, the corresponding portion of the copolymer chains will contain relatively fewer alanine amino

³⁵ Zelzer M and Heise A, Determination of copolymerization characteristics in the N-carboxy anhydride polymerization of two amino acids, *Polymer Chemistry*, 2013(4), 3896.

³⁶ See Section II.B.1 above.

³⁷ We have observed this conservation based upon analyses of Copaxone conducted by ANDA applicants and submitted in connection with ANDAs as well as from FDA's own internal laboratory analyses of samples of Copaxone.

acids, as compared to the initial portion of the copolymers. Conversely, as NCA-tyrosine is only slowly being incorporated into the copolymer, its relative concentration to other NCA-amino acids will be enriched over the course of the polymerization reaction and its relative rate of incorporation into the polymer will increase. Therefore, during the later phases of chain propagation, the corresponding portion of the copolymer chains will be enriched with tyrosine, as compared to the initial portion of the copolymers.³⁸

As described above, the propagational shift is a key characteristic of the polymerization step. The shifting of rates of incorporation into the copolymer chains as measured in this progression is governed by the reaction kinetics (i.e., the intrinsic reactivities and concentrations of the reactants) of the reaction solution and therefore is not a random event. Due to the non-random nature of the reaction, the chance of producing a conserved local amino acid sequence is increased, which is consistent with the conservation of local sequences between batches of Copaxone. There are many different factors that can affect the propagational shift (e.g., reaction scheme, reactant concentrations, and reaction conditions). To establish the active ingredient sameness and to ensure equivalence of conservation of local sequences, a proposed generic glatiramer acetate should not only have propagational shift in its synthesis of the copolymer chains, but also needs to have the same propagational shift as in Copaxone.³⁹

Partial Depolymerization. As discussed above, glatiramer acetate polymerization creates amino acid sequences containing tyrosine, glutamic acid, alanine, and lysine in the intermediate copolymer chains that are not completely random, but rather are determined by the relative incorporation rates of the different NCA-amino acids. These copolymer chains, however, are not the final chains present in glatiramer acetate. The manufacturing process used to synthesize glatiramer acetate involves a second step, termed “partial depolymerization,” in which the intermediate copolymer chains are cleaved until the characteristic molecular weight distribution of glatiramer acetate is achieved.⁴⁰ We note that this depolymerization is simply a cleavage step (i.e., breaking the intermediate copolymers into smaller fragments) that does not rearrange the amino acid sequences of the copolymers in any way.⁴¹

³⁸ We note that a similar phenomenon and analysis applies to the amino acids of intermediate reactivities, lysine and glutamic acid, during both the initial and later phases of polymerization.

³⁹ The batch-to-batch variability of Copaxone is considered when structural signatures of propagational shift (see Section III.C) are measured and compared to proposed generic drug products.

⁴⁰ See note 23.

⁴¹ We note that, although not a sequence modification, a pyroglutamate residue may be formed in the place of a glutamic acid residue during partial depolymerization, as a result of the chain carboxylate of a glutamate residue cyclizing with its amine group when the glutamate is located at a newly formed N-terminus resulting from a cleavage reaction during the partial depolymerization.

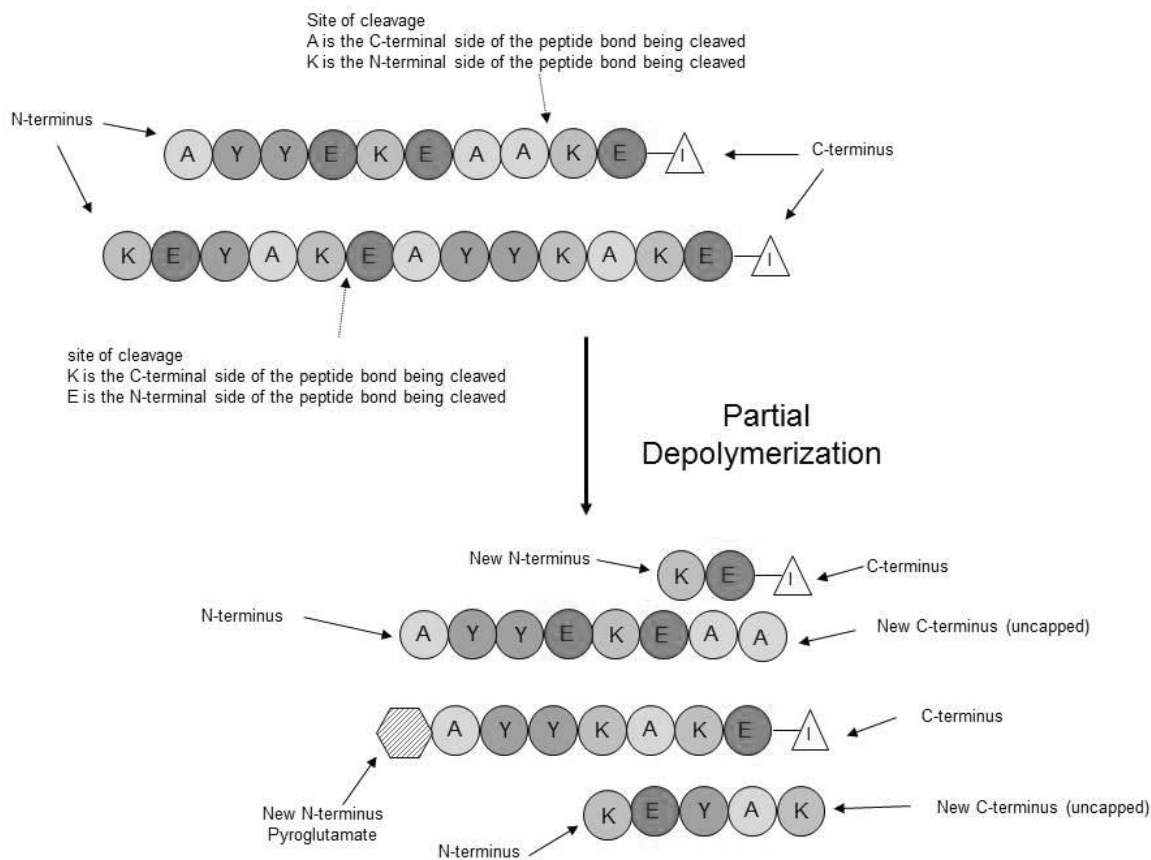


Figure 4. Depiction of the partial depolymerization of the intermediate copolymer used in the manufacture of glatiramer acetate. After depolymerization, the C-termini will be composed of initiator adduct as well as free carboxyl (uncapped) termini, while the N-termini will be composed of Y-tyrosine, E-glutamic acid (or in some cases, a variant pyroglutamate), A-alanine and K-lysine.

In addition to establishing the characteristic molecular weight distribution of Copaxone, there are two other noteworthy aspects of the partial depolymerization process. First, the depolymerization reaction introduces new C-termini at the end of glatiramer chains (see Figure 4), which, unlike the “capped” initiator C-termini generated during the initial polymerization step, have free carboxylate groups. Most notably, because each cleavage introduces a new “uncapped” (amino acid residue with free carboxylate) C-terminus to the copolymer mixture, the ratio of “uncapped” C-termini versus “capped” (amino acid residue with initiator) C-termini is a key characteristic of depolymerization related to the number of cleavage events that take place during this partial depolymerization step, which is incorporated into the active ingredient sameness criteria described below.

Second, the reaction mechanism of the depolymerization or cleavage step may be to some degree chemically selective,⁴² meaning that there may be some degree of preferential cleavage between specific pairs of certain amino acids. The degree and type of any selectivity of the cleavage determines the relative amino acid composition of resultant newly formed N and C termini. For example in Figure 4, where cleavage occurs between lysine and alanine, the resultant newly formed alanine at the C-terminus and lysine at the N-terminus would be a direct reflection of any cleavage preference at the C and N terminal sides of an alanine-lysine peptide bond during partial depolymerization of the intermediate copolymer. The profile of amino acid residues at the newly formed N-termini and C-termini is another key characteristic of the partial depolymerization because it reflects the degree and type of any selectivity of cleavage present in a given depolymerization reaction. Specifically, the proportions of amino acids present at the N-termini of glatiramer acetate (position 1) reflect any biases to cleavage at the N terminal sides of peptide bonds during partial depolymerization. Likewise, the proportions of amino acids present in position 1 of uncapped C-termini of glatiramer reflect any biases to cleavage at the C terminal sides of peptide bonds during partial depolymerization.

Finally, as noted above, due to propagational shift, there will be different proportions of amino acids (and their local sequences) along the copolymer chains. Therefore, if, and to the extent, a selectivity of cleavage based upon amino acid N and C peptide terminal side preferences exists, differing regions of the intermediate copolymer chain may have differing propensities for cleavage based upon the varying composition of amino acids along the length of the copolymer. The interaction between these two unique process characteristics, propagational shift and any selective cleavage, ultimately determine the distribution of local sequences in the copolymer mixture of glatiramer acetate, creating unique structural characteristics of Copaxone, which are incorporated into the active ingredient sameness criteria described below.

In conclusion, the amino acid chains formed through polymerization in the synthesis of glatiramer acetate are not completely random, but rather are a reflection of the physicochemical properties of starting materials and the fundamental chemistry used to manufacture glatiramer acetate, including polymerization of activated amino acids with an initiator to yield an intermediate copolymer, followed by partial depolymerization. The distribution of amino acid sequences is governed by these chemical reactions, including the relative rates of reaction between the amino acids during initiation and chain propagation during polymerization and cleavage during partial depolymerization. More specifically, the amino acid sequences present in glatiramer acetate are dictated by the interplay of polymerization initiation, propagational shift

⁴² Chemical selectivity refers to, among other things, a bias for cleavage in the glatiramer acetate copolymer chains taking place at certain specific amino acid residues. Any chemical selectivity of the depolymerization step will influence the resultant sequences of the cleaved copolymer chains. To illustrate, a single glatiramer acetate copolymer chain with a sequence of KAYEAKAA may be depolymerized via a process having a chemical selectivity with a bias to cleave adjacent to the E (glutamic acid) residue, resulting in two fragments, KAY and EAKAA. Note that there is no rearrangement of the sequences during such a depolymerization reaction, but the extent of any chemical selectivity of depolymerization affects the final distribution of resultant copolymer chains. Note also that the foregoing holds whether or not the selectivity is simply a bias to cleavage (e.g., that the chain KAYEAKAA may also be cleaved in different ways, albeit with a lower probability, such as into fragments KA, YEAK, and AA), rather than cleaving in the same manner in every instance.

during polymerization and cleavage (including the number of cleavage events and any selectivity) during partial depolymerization. This fundamental chemistry used in the manufacturing process, the characteristics of which can be captured analytically, constitutes a key element in establishing active ingredient sameness between a generic glatiramer acetate injection and the RLD, as further described below.

III. GENERIC GLATIRAMER ACETATE INJECTION CAN CONTAIN THE SAME ACTIVE INGREDIENT AS COPAXONE

Section 505(j)(2)(A)(ii)(I) of the Federal Food, Drug, and Cosmetic Act states that, for a single active ingredient drug product, an ANDA must contain information to show that the active ingredient⁴³ of the generic drug product is the “same” as that of the listed drug.⁴⁴

Thus, an ANDA applicant for a generic version of Copaxone must provide sufficient information to show that the proposed drug product contains the same active ingredient as Copaxone. Glatiramer acetate is an array of diverse peptide copolymers, and this presents a complexity in terms of demonstrating active ingredient sameness. Not only does this array of copolymers create a chemically complex product, but a determination of active ingredient sameness cannot focus on any one portion or fraction of glatiramer acetate, but must be applied to the array of copolymers as a whole.⁴⁵ Thus, in order to demonstrate active ingredient “sameness,” we expect

⁴³ FDA regulations (at 21 CFR 210.3(b)(7)) provide that “[a]ctive ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.” FDA regulations (at 21 CFR 314.3(b)) also provide that “*drug substance* means an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates use[d] in the synthesis of such ingredient.” See also Proposed Rule: Abbreviated New Drug Applications and 505(b)(2) Applications, 80 FR 6802, 6811 (Feb. 6, 2015) (proposing to add the definition of “active ingredient” currently in 21 CFR 210.3(b)(7) to 21 CFR 314.3(b)).

⁴⁴ FDA regulations define “same as” to mean “identical in active ingredient(s).” 21 C.F.R. § 314.92(a)(1). In the preamble to this final rule, FDA rejected the suggestion that, to be the same as the listed drug’s active ingredient, the ANDA product’s active ingredient must “exhibit the same physical and chemical characteristics, that no additional residues or impurities can result from the different manufacture or synthesis process; and that the stereochemistry characteristics and solid state forms of the drug have not been altered.” 57 Fed. Reg. 17,950 at 17958-59 (Apr. 28, 1992). Instead, FDA “will consider an active ingredient to be the same as that of the reference listed drug if it meets the same standards for identity.” *Id.* at 17,959. FDA explained that “[i]n most cases, these standards are described in the U.S. Pharmacopeia (U.S.P.). However, in some cases, FDA may prescribe additional standards that are material to the ingredient’s sameness.” *Id.* In this instance, there is no USP monograph for glatiramer acetate, and OGD has described the appropriate standards for identity (or criteria for active ingredient sameness) in this memorandum.

⁴⁵ Teva asserts that our sameness analysis cannot focus exclusively on any one quality of Copaxone (e.g., First Citizen Petition at 19-20, Second Citizen Petition at 3, 13-15, 16, 22-23; Third Citizen Petition at 3; Fourth Citizen Petition at 4, 5, 6; Sixth Citizen Petition at 8 and Jan. 27, 2014 Supplement to Sixth Citizen Petition at 6-8). We agree that active ingredient sameness must be considered holistically, but on different grounds than Teva, as

the diversity (including the conserved aspects) of a generic glatiramer acetate to be shown to be equivalent to that of the active ingredient in Copaxone.

Although currently there is no single physicochemical or biological characterization that can demonstrate active ingredient sameness between a generic glatiramer acetate injection and Copaxone, there is a battery of characterizations that, when combined, can be applied to comparatively characterize the glatiramer acetate and provide a collection of scientific evidence sufficient to establish active ingredient sameness.⁴⁶ This collection of evidence is obtained from orthogonal measurements, which are complementary in nature. Therefore, when considered as a whole rather than piece-by-piece, generic glatiramer acetate can be shown to have the same composition and diversity of amino acid sequences and of peptide copolymers as the active ingredient in Copaxone. Based on our current understanding of the product, its indication and its mechanisms of action, this can be accomplished by showing equivalence between the ANDA product and RLD as to the following criteria:

1. Fundamental reaction scheme;
2. Physicochemical properties including composition;
3. Structural signatures for polymerization and depolymerization; and
4. Results in a biological assay.

These four criteria take into account the inherent molecular diversity associated with glatiramer acetate and, taken together, are designed to provide overlapping and confirmatory evidence of active ingredient sameness through which OGD can conclude that generic glatiramer acetate injection has the same active ingredient as Copaxone.⁴⁷ As noted above, the first three criteria provide evidence to identify and increasingly refine the information supporting active ingredient sameness, while the fourth criterion serves as confirmation of the initial three criteria. Importantly, we note that we do not recommend that an ANDA applicant show that based on these four criteria, any given batch of the product described in its ANDA is identical to any

explained in this memorandum. Further, we note that these criteria are different in scope from, and serve a different function than, the manufacturing controls that Teva claims “provide information on Copaxone’s bulk properties and do not elucidate the specific sequences and structures that constitute the active ingredient.” (Sixth Citizen Petition at 32.) These criteria, when taken in concert and as further explained below, establish active ingredient sameness.

⁴⁶ We note that we disagree with Teva’s assertion that Copaxone is insufficiently characterized to make a determination of active ingredient sameness, as we describe throughout this memorandum (Second Citizen Petition at 20 and Jan. 27, 2014 Supplement to Sixth Citizen Petition at 6-8).

⁴⁷ Several assertions made by Teva in its Citizen Petitions relate to Teva’s position that the overlapping criteria for sameness established by the Agency in connection with enoxaparin should not be applicable to Copaxone (e.g., Third Citizen Petition at 5, 9, 10, 14, 15; Sixth Citizen Petition at 27-28, referencing Letter from Throckmorton, D., Docket No. FDA-2003-P-0273 (July 23, 2010) (“Enoxaparin Petition Response”)). We note, however, that while overlapping criteria have been adopted, the specific overlapping criteria described herein are different than for enoxaparin, and have been uniquely designed for, Copaxone, to take into account the nature of the active ingredient glatiramer acetate. On a related note, several of Teva’s assertions relate to the inadequacy of certain of the foregoing criteria in isolation (e.g., First Citizen Petition at 22, 23; Third Citizen Petition at 12-13, 14, 16-17; Sixth Citizen Petition at 35 and Jan. 27, 2014 Supplement to Sixth Citizen Petition at 6-8); however, these assertions do not challenge the adequacy of all of these criteria when considered in concert.

single batch of the RLD. This is consistent with the nature of Copaxone, which has inherent batch-to-batch variability.⁴⁸ Rather, we evaluate active ingredient sameness by considering the level of variability in the RLD compared to that of the proposed generic product.⁴⁹ A sameness evaluation of these criteria will be based upon qualitative and/or quantitative comparisons of a generic glatiramer acetate injection to multiple batches of Copaxone, taking into consideration the batch-to-batch variability, sampling of Copaxone, and analytical test variability.

A. Equivalence of Fundamental Reaction Scheme

The first criterion of sameness is to ensure that the active ingredient of a generic glatiramer acetate injection is produced by an equivalent fundamental reaction scheme.^{50, 51, 52} As noted above, a fundamental reaction scheme for the manufacture of glatiramer acetate has been published and features the polymerization reaction involving the activated amino acids and initiator, followed by a partial depolymerization. As published, the first step of polymerization involves the polymerization of NCA-tyrosine, NCA-alanine, NCA-glutamate,⁵³ and NCA-lysine⁵⁴ with an initiator. In addition, the step of partial depolymerization is based upon acid

⁴⁸ The statutory requirement of sameness “must be read in the context of the kind of drug at issue,” and “does not unambiguously require . . . complete chemical identity.” *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1319-20 (D.C. Cir. 1998) (noting that batch-to-batch variability of a reference product “would make the target of the comparison . . . indeterminate” if “absolute chemical identity were required.”).

⁴⁹ This is in contrast to certain assertions made by Teva in its Citizen Petitions that, in effect, a determination of sameness would require a finding that a generic glatiramer acetate injection and Copaxone are identical (e.g., Second Citizen Petition at 11; Third Citizen Petition at 4, 7; Fourth Citizen Petition at 6, 9, 10; Sixth Citizen Petition at 8, 25, 30, 32, 34). However, we note that given the batch-to-batch variation inherent to Copaxone, the RLD itself is not identical between batches. As such, active ingredient sameness criteria for a generic glatiramer acetate injection should incorporate this batch-to-batch variation.

⁵⁰ The critical importance of the well-controlled synthesis process is also highlighted by certain of Teva’s assertions in its Citizen Petitions (e.g., First Citizen Petition at 12, 13; Fourth Citizen Petition at 5; Sixth Citizen Petition at 8 and Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 4, 10-11). Teva’s manufacturing process for Copaxone is also emphasized in a citizen petition submitted by Peptimmune, Inc. (Docket No. FDA-2010-P-0531) (Peptimmune Citizen Petition), at 27.

⁵¹ Several of Teva’s assertions in its Citizen Petitions suggest that, given Copaxone’s complexity, its manufacturing process cannot be reverse-engineered (e.g., Fourth Citizen Petition at 5; Sixth Citizen Petition at 30 and Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 3, 4, 9-10). As described above, we disagree. By using publicly available information regarding the synthesis process coupled with the sensitivity and diagnostic capabilities of the structural signatures, a synthesis process can be established that results in an active ingredient that is the same as the active ingredient of Copaxone, which then may be further confirmed as described below.

⁵² We note that, as discussed in the relevant OGD/Office of Pharmaceutical Quality (OPQ) review documents for its ANDA, Sandoz established equivalence of this criterion using a fundamental reaction scheme for the synthesis of its glatiramer acetate equivalent to that published with respect to the RLD.

⁵³ In this document, we use NCA-Glutamic Acid and NCA-Lysine to denote N-carboxyanhydrides of γ -benzyl glutamate, and ϵ , N-trifluoroacetyllysine respectively. The side chain protecting groups are implicitly included in the notation.

⁵⁴ *Id.*

catalyzed cleavage.⁵⁵ An ANDA applicant may satisfy this first criterion of active ingredient sameness by using the same (or equivalent): (1) NCA-amino acids and polymerization initiator to yield the intermediate copolymer and (2) chemical reagent(s) for acid-catalyzed cleavage conditions. As discussed above, the amino acid sequences present in glatiramer acetate are not entirely random, but are dictated by the polymerization and partial depolymerization steps used in its manufacturing process. More specifically, the amino acid sequences present in glatiramer acetate are dictated by the interplay of polymerization initiation, propagational shift in chain propagation during polymerization, and the cleavage reactions in partial depolymerization.

Therefore, if an ANDA applicant uses the same (or equivalent) NCA-amino acids and initiator to yield the intermediate copolymer, then the synthesis reactions (including the underlying chemical kinetics involved to initiate the polymerization and to propagate the copolymer chains) will be qualitatively equivalent to those used to synthesize the intermediate copolymer used to produce Copaxone. Moreover, if an ANDA applicant uses the same (or equivalent) chemical reagent(s) for acid-catalyzed cleavage conditions, the depolymerization reaction (including any cleavage selectivity) will be qualitatively equivalent to that used to produce Copaxone.⁵⁶

The elements of a fundamental reaction scheme to manufacture glatiramer acetate can be determined and confirmed using publicly available information on the synthesis process⁵⁷ in conjunction with diagnostic analysis of the RLD by orthogonal analytical measurements, as described below in connection with the remaining active ingredient sameness criteria. Using the same (or equivalent) fundamental reaction scheme is essential to the sameness criteria because doing so can ensure the qualitative, although (if used in isolation) not the quantitative, equivalence of the chemical kinetics used in glatiramer acetate synthesis, which in turn dictates the key characteristics (i.e., propagational shift and cleavage pattern) in glatiramer acetate.

As noted above, we do not, consider this criterion alone to be sufficient to establish active ingredient sameness because, for example, employing the same (or equivalent) reaction scheme can only ensure a qualitatively equivalent propagational shift exists between a generic glatiramer acetate and the glatiramer acetate in Copaxone. As we discussed previously in Section II.B.2, the precise characteristics of the propagational shift can be affected by reaction conditions and other manufacturing process parameters. Therefore, while we consider equivalence of fundamental reaction scheme to be one of four criteria used to determine active ingredient sameness for glatiramer acetate, based on our current understanding, used alone, this would be insufficient to ensure active ingredient sameness. The additional criteria are described as follows.

⁵⁵ See note 23, for example.

⁵⁶ As discussed below, qualitative equivalence of these reactions does not necessarily mean that they are quantitatively equivalent. Equivalence of the fundamental reaction scheme, in conjunction with equivalence as to the remaining active ingredient sameness criteria, establishes that the RLD and ANDA synthesis and depolymerization reactions are both qualitatively and quantitatively equivalent.

⁵⁷ See notes 22 and 23, for example.

B. Physicochemical Properties, Including Composition

The second criterion for demonstrating active ingredient sameness of generic glatiramer acetate injection to Copaxone is equivalence of physicochemical properties, which include, but are not limited to, molecular weight distribution, amino acid composition, and spectroscopic fingerprints.⁵⁸ Properties such as these provide broad, but critical, characterizations that are able to confirm (1) active ingredient sameness at a greater level of quantitative detail and (2) equivalence of underlying reaction processes to a greater degree than may be guaranteed by the first criterion alone.⁵⁹ As noted above, it is the combination of these two equivalence criteria with the two remaining criteria discussed further below, which add complementary evidence of active ingredient sameness on both a detailed chemical level and a broader, system-wide level.

Amino Acid Building Blocks. Glatiramer acetate is a mixture of peptide copolymers containing four specific amino acids in a defined molar ratio. The amino acids present in the glatiramer acetate are L-glutamic acid, L-lysine, L-alanine, and L-tyrosine, with an average molar fraction of 0.141, 0.338, 0.427, and 0.095, respectively. The amino acid content of glatiramer acetate can be determined by complete hydrolysis of the mixture to its amino acid components⁶⁰ and, for purposes of establishing active ingredient sameness, the content should be equivalent to that of the RLD. In addition, the optical purity (i.e., chirality) of the four amino acids, which may be affected by certain manufacturing process conditions, should be measured and compared to the values found in Copaxone.⁶¹

Molecular Weight Distribution. Glatiramer acetate is a synthetic copolymer having an average molecular weight of between 5-9 kDa. For the purposes of demonstrating sameness, it is essential for generic glatiramer acetate to have an array of chain lengths equivalent to that of the RLD. Comparing molecular weight distributions, including the molar mass moments (Mn, Mw, Mz) and polydispersity (Ip) for the generic drug and the RLD can be accomplished by using a variety of techniques including size exclusion chromatography, mass spectroscopy, or other appropriate methods.

⁵⁸ We note that, as discussed in the relevant OGD/OPQ review documents for its ANDA, Sandoz established equivalence of these properties between its glatiramer acetate injection and the RLD.

⁵⁹ Several of Teva's assertions made in its Citizen Petitions indicate that individual characteristics of a proposed generic glatiramer acetate (e.g., average molecular weight) would not, alone, be sufficient to support a determination of sameness with respect to Copaxone (e.g., First Citizen Petition at 22, 23, Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 6, 7, 8; Nov. 13, 2014 Supplement to the Seventh Citizen Petition at 4). Similar assertions are also made in the Peptimmune Citizen Petition, at 27. We underscore that, as described above, this is not the approach adopted by OGD and that the overlapping criteria together are used to establish active ingredient sameness.

⁶⁰ For example, after treatment with concentrated hydrochloric acid at 100 °C for 24 hours, the amino acid mixture can be treated with o-phthalaldehyde (OPA) and the derivatized residues may then be identified and quantitated by using ion exchange or reverse phase chromatography.

⁶¹ The amino acids can exist in two chiral configurations (i.e., L and D). Given that the constituent amino acid building blocks in Copaxone are in the L-configuration, the amino composition in a generic composition should likewise be in the L-configuration.

Spectroscopic Fingerprints. To demonstrate equivalence of physicochemical properties, it is important to obtain information relating to the overall properties of the drug, as measured by spectroscopy, which must be equivalent when generic glatiramer acetate injection is compared to Copaxone, the RLD. Such spectroscopic methods (e.g., nuclear magnetic resonance (NMR) spectra,⁶² Fourier transform infrared spectroscopy (FT-IR) or other similar methods) can provide “spectroscopic fingerprints” of molecules, which are measurements of the emission or absorption of light by certain functional groups (e.g., carbonyl and hydroxyl groups by FT-IR) or certain elements (e.g., ¹H and ¹³C by NMR) in different functional groups contained within a drug.⁶³ These measurements are sensitive to the chemical environments within and around such molecules (i.e., glatiramer acetate copolymers). Equivalence between a generic glatiramer acetate active ingredient and the active ingredient of the RLD using spectroscopic fingerprints can further ensure the identity and composition of the copolymers.

Furthermore, circular dichroism (CD)⁶⁴ is a spectroscopic method commonly used to study secondary structures in polypeptides. Secondary structures and their thermal stability are primarily determined by the amino acid sequence and length of a given polypeptide.⁶⁵ Given this, analysis of CD spectra can be used as a method to determine the distribution of secondary structure types (e.g., alpha helix and beta sheet) in a glatiramer acetate injection.⁶⁶ Equivalence achieved in the CD study of a generic glatiramer acetate active ingredient and the active ingredient of the RLD demonstrates equivalence in secondary structures and the related amino acid sequence information.⁶⁷

⁶² Both one dimensional and two dimensional nuclear magnetic resonance spectra could be employed.

⁶³ See Dwyer J, Zhou M. Polymer Characterization by Combined Chromatography-Infrared Spectroscopy. International Journal of Spectroscopy (2011). See also, Koenig J, Spectroscopic Characterization of Polymers, Analytical Chemistry, 1987; 59(19): 1141A.

⁶⁴ In the far-ultraviolet (UV) region (195-245 nm), the CD spectra of polypeptides are sensitive to secondary structure. Variations in secondary structure perturb the CD signature of the amide bond in this region and models for the spectrum of each type of secondary structure have been established.

⁶⁵ We note that, based on our current understanding, Copaxone exists in a thermodynamically stable, reversible equilibrium state, meaning that the criteria for determining active ingredient sameness described herein are sufficient without additional characterizations of any higher order structure of glatiramer acetate. This has been confirmed by data submitted by Sandoz in connection with its ANDA in which it utilized differential scanning calorimetry, a measurement of heat capacity as a function of temperature to show the product’s thermodynamic stability, in combination with testing that revealed no difference in the biological activity of chemically denatured and renatured product as compared to untreated product. (The biological assay used in this instance was the EAE assay, which is described in greater detail below.) Additional data submitted by Sandoz resulting from the analysis of CD spectra (see following note) also confirm this conclusion.

⁶⁶ A CD spectrum is composed of a population-weighted, linear combination of the theoretical pure secondary structures. The interpretation of the secondary structure content can be achieved by deconvoluting a CD spectra into the sum of components from each of its secondary structure type components, namely random coil, alpha helix, and beta sheet structures.

⁶⁷ CD spectra may also be able to show equivalence of thermal stability over a temperature range.

Taken together, overall characterizations of physicochemical properties provide important supporting evidence of active ingredient sameness that is complementary to the other criteria when a generic product is compared to the RLD. Given this, this criterion is also a critical element of establishing active ingredient sameness.

C. Equivalence of Structural Signatures for Polymerization and Depolymerization

As discussed above, the composition and sequence diversity of peptide copolymers in Copaxone are governed by the polymerization and depolymerization reaction kinetics used in its synthesis. Although a fundamental reaction scheme for manufacturing glatiramer acetate is published in the literature,⁶⁸ other relevant information (including specific process conditions) by which Teva manufactures glatiramer acetate are not publicly available.⁶⁹ If the same fundamental reaction scheme is followed, but if certain other process conditions are not incorporated or considered, the produced glatiramer acetate active ingredient may achieve “qualitative” similarity with the characteristics of the polymerization and depolymerization reactions, but may not, however, be the same as the RLD.⁷⁰ Using propagational shift as an example, as described above, a generic applicant need not only show that its product was synthesized with a process resulting in a propagational shift, but such an applicant also needs to demonstrate that the propagational shift resulting from its process is the same as the propagational shift present in the RLD, as measured by characterizations and comparisons between the proposed generic and the RLD products.

Within the reaction schemes described above, certain characteristics of the reaction leave what is referred to in this memorandum as “structural signatures” in the active ingredient, including initiation chemistry of peptide chains, coupling between the various amino acid pairs during the chain propagation and any cleavage preference of depolymerization. Therefore, to ensure active ingredient sameness between a generic glatiramer acetate injection and the RLD, and specifically to ensure equivalent polymerization initiation, propagational shift and partial depolymerization of the glatiramer acetate, ANDA applicants would need to identify and analyze structural signatures that are chemical attributes of glatiramer acetate and correlate to both the polymerization step (including initiation kinetics and propagational shift) and the cleavage step of partial depolymerization.⁷¹ Measuring structural signatures of generic glatiramer acetate in

⁶⁸ See notes 22 and 23.

⁶⁹ For example, the polymerization initiation and propagational shift in the first polymerization step may be dependent on process conditions such as temperature, concentration of NCA amino acids and initiator. Likewise, the cleavage reactions during the partial depolymerization may be dependent on process conditions such as temperature, time, concentrations of hydrogen bromide, acetic acid, and water.

⁷⁰ We note that the approach taken here is not inconsistent with, and addresses, arguments made by Teva in its citizen petitions regarding the impact of variations in the process parameters used in the manufacture of glatiramer acetate, as further explained here and elsewhere. (See, e.g., Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 4.)

⁷¹ We note that an analogous concept was used in connection with establishing active ingredient sameness criteria for enoxaparin, however, as described in this memorandum, the signatures to be used in connection with glatiramer acetate are unique to glatiramer acetate and are more extensive than those used in connection with enoxaparin. For example, we note that the sameness criteria in the case of enoxaparin focused on one primary step of its synthesis

comparison to the same structural signatures of the active ingredient in the RLD provides evidence of active ingredient sameness as well as detailed, quantitative equivalence of the underlying reaction chemistry and kinetics. Such equivalence of the underlying reaction chemistry and kinetics, in turn, provides further confirmation of active ingredient sameness between the generic product and the RLD. Thus, in combination with the other sameness criteria described in this document, equivalence of these structural signatures ensures that the resultant molecular identity and diversity of amino acid sequences in generic glatiramer acetate's copolymer chains will be equivalent to those of the active ingredient in Copaxone.

To demonstrate active ingredient sameness, structural signatures should cover the critical process steps of (1) polymerization initiation, (2) propagational shift during polymerization and (3) cleavage during partial depolymerization. We anticipate that each ANDA applicant will develop its own set of structural signatures for its generic product and will compare these signatures to the RLD.⁷² Each applicant will also provide information to support the validity of its proposed structural signatures and the corresponding methods, which can be supported, for example, by (a) a mechanistic understanding of the synthetic process, (b) published literature, (c) pharmaceutical development studies that link changes in the ANDA manufacturing process to the corresponding structural signature, (d) negative control studies that introduce variations in the process and corresponding variations to the resulting product and structural signatures and (e) the proposed equivalence range/acceptance criteria⁷³ should be based on the batch-to-batch variations of the RLD product. Examples of structural signatures for polymerization initiation, propagational shift and the cleavage reactions of partial depolymerization are discussed in greater detail below.

1. Structural Signatures for Polymerization Initiation

As discussed in Section II.B.2, the use of a polymerization initiator in the first step of glatiramer acetate synthesis is described in the method documented in Teva's patents and the published literature. There are two characteristics of polymerization initiation, which should be captured as structural signatures:

(i.e., cleavage), whereas in this instance, the sameness criteria focus on multiple aspects of the synthesis of glatiramer acetate, including initiation, polymerization and partial depolymerization. See, e.g., Lee S, Raw A, Yu L, Lionberger R, Ya N, Verthelyi D, Rosenberg A, Kozlowski S, Webber K, Woodcock J. Scientific considerations in the review and approval of generic enoxaparin in the United States. *Nature Biotechnology* 2013 (31) 220-226. See also Enoxaparin Petition Response.

⁷² We note that, as discussed in the relevant OGD/OPQ review documents for its ANDA and in certain cases below, Sandoz developed such structural signatures and established equivalence of such signatures between its glatiramer acetate injection and the RLD in connection with its ANDA.

⁷³ Teva seems to assert in its Third Citizen Petition that a sameness determination for Copaxone would require a finding that specific sequences found in a generic glatiramer acetate injection and the RLD are identical (at 17-18). (See also Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 6-8.) As described above, OGD's approach instead is to ensure equivalence of diversity and distribution of sequences. This equivalence, when taken in concert with the other criteria described in this memorandum, is sufficient to ensure active ingredient sameness.

- a) the distribution (i.e., relative amounts) of the four amino acid-initiator adducts; and
- b) the initiator content in copolymer.

The first property reflects the bias of amino acid incorporation upon initiation based on the initiation kinetics, including the intrinsic reactivity of each NCA-amino acid with the initiator and the concentration contributions of the four NCA-amino acids during the initiation stage. The second property, correlated with the relative number of copolymer chains initiated in the reaction, can also be correlated to the average chain length of the intermediate copolymer. Both properties have significant impacts on the propagation of polymerization and partial depolymerization.

2. Structural Signatures for Propagational Shift During Polymerization

As discussed above, the amino acid composition (i.e., molar ratios of the four amino acids) will not be uniform across the intermediate copolymer chain, but instead will differ along its length due to the phenomenon of propagational shift (also described above), which arises primarily due to the differences in relative intrinsic reactivities and relative concentrations among the four NCA-amino acids. As noted above, a structural signature for propagational shift is particularly important, as it plays a critical role in determining the distribution of local sequences in the glatiramer acetate copolymers and impacts the locations of potential cleavage sites for the subsequent depolymerization step to the extent of any cleavage preference. A generic sponsor should identify relevant amino acid sequence properties and corresponding analytical procedures, which can quantitatively measure the propagational shift in Copaxone.

In the case of Sandoz's ANDA, the applicant developed several analytical approaches to characterize propagational shift in the manufacturing process of glatiramer acetate. After reviewing, OGD found these structural signatures acceptable.⁷⁴ To summarize, Sandoz's structural signature for propagational shift was based in its finding that the effect of propagational shift is produced during the formation of the intermediate copolymer, and can be measured at the N-termini. Because, however, Sandoz (and other generic applicants generally) do not have access to Teva's intermediate copolymer for analysis or comparison, the structural signature for propagational shift would instead need to be established using analysis and comparison of the further processed final product of Copaxone, rather than the intermediate copolymer. To this end, Sandoz then established that the effect of propagational shift on amino acid compositions is still measurable at the N-termini of the glatiramer acetate drug product after the partial depolymerization from position 2 (as measured from the N-terminus) onward.⁷⁵ Analytically, this structural signature was measured using peptide N-terminal sequencing by

⁷⁴ Note that a more detailed review of the structural signatures developed and utilized by Sandoz in its ANDA is found in the OPQ Chemistry Reviews for this ANDA. The general description here serves primarily to illustrate an example of a structural signature for propagational shift.

⁷⁵ The identity of the amino acid at position 1 would be impacted both by any cleavage bias as well as by propagational shift. As a result, the effect of propagational shift at position 1 may be less specific.

Edman degradation⁷⁶ and was validated as a structural signature through the design, synthesis and testing of various negative controls.⁷⁷

In addition, Sandoz established another structural signature to empirically compare propagational shift between its glatiramer acetate and Copaxone. In this instance, the copolymer chains in each glatiramer acetate drug product were first fractionated based on their size/molecular weight using size exclusion chromatography (SEC) into different fractions. Then amino acid composition analysis was performed on each fraction. The resulting structural signature is an amino acid composition distribution for each fraction of copolymer separated as a function of molecular weight, which was also validated by well-designed negative controls. This structural signature, although more of an empirical comparison of propagational shift found in the RLD and the proposed generic product than the signature described above (which has more strongly established ties to the underlying mechanism of chemistry), serves as further confirmation of propagational shift.

3. Structural Signatures for Cleavage Reactions in Partial Depolymerization

As described above, in partial depolymerization of glatiramer acetate, the copolymers are cleaved until the characteristic length or molecular weight distribution of the chains is achieved. In each cleavage reaction, new N- and C- termini are formed. This process allows the development of structural signatures for the cleavage reactions of the depolymerization step. These structural signatures are intended to characterize any preference at the site of cleavage and the average number of cleavages for an intermediate copolymer chain. Details of examples of such structural signatures⁷⁸ include:

- First, because the amino acids at position 1 of the N-termini result from a cleavage reaction, the relative proportion of amino acids present at position 1 of the N-termini of glatiramer acetate reflects potential cleavage biases at peptide bonds with such amino acids present at the N-terminal side during partial depolymerization;
- Similarly, because at least a portion of the amino acids at position 1 of the “uncapped” C-termini result from a cleavage reaction, the relative proportion of amino acids present at position 1 of the “uncapped” C-termini of glatiramer acetate reflects potential relative cleavage biases at peptide bonds with such amino acids present at the C-terminal side during partial depolymerization; and

⁷⁶ Edman degradation acts on the N-terminal sequence of a polypeptide. In the reaction, the N-terminal residue of a polypeptide is labeled with phenylisothiocyanate and is then cleaved under mildly acidic conditions. Peptide bonds in the remainder of the polypeptide are not cleaved during this process. The resultant, derivatized N-terminal amino acid residue can be identified by chromatographic methods. Berg JM, Tymoczko JL, Stryer L. *Biochemistry*. Sixth ed. New York: W.H. Freeman and Company; 2007.

⁷⁷ We note that because of the further processing of the intermediate copolymer into the final product (primarily as a result of partial depolymerization), the effect of propagational shift in the final product is, although measurable, attenuated as compared to the effect of the shift in the intermediate copolymer.

⁷⁸ We note that, as discussed in the relevant OGD/OPQ review documents for its ANDA, Sandoz established equivalence in these structural signatures between its glatiramer acetate injection and the RLD.

- Finally, because each cleavage reaction introduces a new “uncapped” C-terminus, the ratio of “uncapped” versus “capped” C-termini correlates with, and serves as a structural signature of, the number of cleavage events that take place during partial depolymerization.

In summary, the structural signature examples discussed above in subsections 1, 2 and 3 capture key characteristics of polymerization (including initiation and propagation) and the partial depolymerization reaction. Specifically, these structural signatures provide quantitative measurements correlated with the amino acid preference of initiation, the average size of intermediate copolymer chains, the propagational shift, any cleavage site preference during partial depolymerization and the average number of cleavages applied to an intermediate chain. Using these structural signatures and the associated acceptance criteria, together with the first two sameness criteria (equivalent fundamental reaction scheme and equivalent physicochemical properties), the active ingredient sameness of glatiramer acetate can be established in terms of both its overall chemistry and in terms of conservation of its sequence diversity.

D. Equivalence of Biological Assay

As described above, the first three criteria for active ingredient sameness ensure that the molecular diversity of copolymers associated with an ANDA product’s active ingredient (glatiramer acetate) are the same as Copaxone’s glatiramer acetate. The fourth criterion serves as a confirmatory test of equivalence and provides complementary confirmation of sameness. As noted above, the activity of glatiramer acetate was originally predicted based upon the effect of glatiramer acetate when tested against experimental autoimmune/allergic encephalomyelitis (EAE). This test has become the primary animal model for multiple sclerosis. In the EAE assay, mice, rats, or guinea pigs treated with a myelin-related, EAE-promoting agent, invariably develop EAE, which is manifested by hind limb paralysis. Glatiramer acetate attenuates the severity of the disease in test animals elicited by the EAE-promoting agent.⁷⁹ Given that it is an established animal model, in addition to the broad array of potential mechanisms of action of glatiramer acetate, the EAE assay⁸⁰ provides a system-wide confirmatory assay for sameness.⁸¹ Equivalence in this assay provides important confirmatory evidence of active ingredient sameness between generic glatiramer acetate injection and the RLD.⁸²

⁷⁹ Stern J, Iles Z, Reddy J, Keskin D, Sheu D, Fridkis-Harrell M, Amelioration of proteolipid protein 139-151 induced encephalomyelitis in SJL mice by modified amino acid copolymers and their mechanism. *Proceedings of the National Academy of Science*, 2004; 101: 11743-11748.

⁸⁰ Teva indicates that it employs an EAE blocking test to assess the consistency of its own batch-to-batch consistency of Copaxone (First Citizen Petition at 24).

⁸¹ Analogous confirmatory bioassays have been previously incorporated into sameness determinations by OGD, including in the cases of enoxaparin and salmon calcitonin. See, e.g., Enoxaparin Petition Response and Lee S, Yu L, Cai B, Johnsons G, Rosenberg A, Cherney B, Guo W, Raw A. *Scientific Considerations for Generic Synthetic Salmon Calcitonin Nasal Spray Products*. *American Association of Pharmaceutical Scientists Journal*. Oct. 2010.

⁸² We note that, as discussed in the relevant OGD/OPQ review documents for its ANDA, Sandoz established equivalence in this assay between its glatiramer acetate injection and the RLD. In addition, as noted above, Sandoz

There are a number of biochemical assays (e.g., T-cell activation, antigen presenting cell activation, anti-glatiramer acetate antibody)⁸³ that measure certain biomarkers through in vitro or in vivo tests to assess the effects of glatiramer acetate. Due to the variability in these tests, and the narrow focus of a particular test compared to the broad potential mechanisms of action of glatiramer acetate, the results of any one such biochemical assay provide less information with respect to active ingredient sameness than the EAE assay.⁸⁴ Therefore, while analysis of data arising out of such biochemical assays may be helpful in assessing an ANDA for a generic glatiramer acetate injection with respect to active ingredient sameness, based on our current understanding of the science, OGD currently considers the EAE assay to be the most useful biological assay for confirmation of active ingredient sameness.

E. FDA Analytical Testing as Confirmation of Sameness Criteria

In addition to the characterizations and assays performed by generic sponsors, FDA's internal laboratory developed and performed its own testing⁸⁵ of multiple batches of Copaxone, the proposed generic glatiramer acetate injection, glatiramer acetate-like products marketed outside of the United States,⁸⁶ and negative controls, in each case using high-resolution analytical techniques. As further described below, these tests validate the findings of, and confirm the robustness of, the sameness criteria described above. The samples were first digested with lysyl endopeptidase, and then the digestion products were analyzed using a liquid chromatography-mass spectrometry (LC-MS) system, allowing for their use as a marker of conserved local sequence information. At the FDA laboratory, a method was developed to analyze the digestion products, where a variant of normal phase liquid chromatography (i.e., hydrophilic interaction liquid chromatography, HILIC) was applied with mass spectroscopy.⁸⁷ Using this approach, over 1000 data points were collected for each sample. Furthermore, a quantitative data analysis method was developed and applied to the data sets collected. This method is sufficiently sensitive such that the batch-to-batch variations of Copaxone can be detected. Based on appropriate statistical analysis of the results, the glatiramer acetate-like products marketed

used the EAE assay to compare activity of a chemically denatured and renatured glatiramer acetate to untreated glatiramer acetate, which assay did not reveal any difference in activity.

⁸³ Teva asserts that certain of these assays should be considered in a sameness determination (e.g., First Citizen Petition at 22-23), but, as described above, we have determined sameness can be established using other criteria.

⁸⁴ This is consistent with several assertions made by Teva in its Citizen Petitions (e.g., Third Citizen Petition at 18, 19; Sixth Citizen Petition at 36).

⁸⁵ We note that FDA has conducted similar testing of other complex drug products (e.g., cyclosporine), in part, to enhance its understanding of these products. See, e.g., Rahman Z, Xu X, Katragadda U, Kirshnaiah Y, Yu L, Khan M. Quality by Design Approach for Understanding the Critical Quality Attributes of Cyclosporine Ophthalmic Emulsion. *Mol. Pharmaceutics* 2014; 11: 787-799.

⁸⁶ Specifically, these include samples of the Natco product marketed in India and Ukraine.

⁸⁷ Other methods of analysis include Reversed Phase (RP) high-performance liquid chromatography (HPLC) with UV detection, which has more limited resolution and sensitivity of the RP-HPLC-UV and allows for qualitative, rather than quantitative, comparison of results.

outside of the United States and negative controls can be clearly distinguished from Copaxone batches. However, when applying the same testing, no significant differences were observed between the proposed generic glatiramer acetate injection under consideration by OGD and Copaxone. In other words, the quantitative characterization of the proposed generic samples is consistent with the same characterization of Copaxone, taking into account its batch-to-batch variability. Because these tests clearly distinguish products that meet active ingredient sameness criteria described above from those that would not meet these sameness criteria, these tests, while not currently considered by OGD to be necessary to establish active ingredient sameness, confirm and validate the robustness of criteria described above to assess the sameness of glatiramer acetate.

F. Conclusion

Copaxone (glatiramer acetate) is one of the few treatments for multiple sclerosis. Glatiramer acetate is comprised of an array of peptide copolymers, and this presents a unique challenge in terms of demonstrating active ingredient sameness between a generic glatiramer acetate injection and Copaxone. However, an ANDA applicant can demonstrate active ingredient sameness to the RLD by using the same (or equivalent) fundamental reaction scheme (developed through public sources and analysis of the RLD), exhibiting equivalence in key physicochemical properties (including composition), identifying and showing equivalence with respect to key structural signatures for polymerization and depolymerization chemistry, and finally demonstrating equivalence in a biological assay. A demonstration that these criteria are satisfied provides compelling evidence that the molecular identity and diversity of glatiramer acetate is equivalent to that of the active ingredient in Copaxone and establishes active ingredient sameness between a generic glatiramer acetate injection and Copaxone.

IV. RESPONSES TO CERTAIN ISSUES RAISED IN CITIZEN PETITIONS

This section addresses certain specific arguments raised by Teva in its citizen petitions.

A. Active Ingredient Sameness

Sameness Criteria in General. In its citizen petitions, Teva has asserted that FDA cannot approve any ANDA that references Copaxone as the RLD because current chemical analytical techniques are incapable of showing that the active polypeptide sequences in a proposed generic product are the same as those in Copaxone.⁸⁸ For example, Teva asserts that it is not possible to demonstrate that generic versions of Copaxone have the same active moieties and are consistent on a batch-to-batch basis. As discussed above in Section III, OGD disagrees with this position. Glatiramer acetate is adequately characterized. Current analytical techniques are capable of supporting a demonstration of active ingredient sameness between the generic glatiramer acetate injection and its RLD.

⁸⁸ For example, First Citizen Petition *supra* note 2 at 19, 25 – 25, 17; Second Citizen Petition at 20 – 24, 35; Third Citizen Petition 10 – 20 (comparing with Enoxaparin); Sixth Citizen Petition 24 – 29, 33 and Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 3, among others referenced elsewhere in this memorandum.

Glatiramer -Like Products and Manufacturing Changes. Teva asserts that slight changes in the manufacturing process for glatiramer acetate can produce altered sequences of unknown safety and efficacy.⁸⁹ Teva asserted that it demonstrated this outcome as it developed a glatiramer -like product known as TV-5010, which was synthesized by using the same four amino acids as are present in glatiramer acetate, but the manufacturing process was varied slightly to produce a higher molecular weight product.⁹⁰ Teva reported that treatment with this higher molecular weight TV-5010 led to toxic side effects not seen with glatiramer acetate. These arguments do not undermine the determinations described in this memorandum. We note that TV-5010 would have failed to satisfy the active ingredient sameness criteria described above. Most obviously, its described molecular weight would have failed to meet the sameness criteria of equivalence of physicochemical characteristics. Teva makes related assertions regarding several “glatiramer-like” products reviewed by regulatory bodies outside of the United States or otherwise not approved by the Agency.⁹¹ We note that these assertions have been considered by OGD in connection with the development and implementation of the sameness criteria described in this memorandum and, regardless of the accuracy of these assertions, they do not alter OGD’s findings described in this memorandum. We note that, as with any ANDA, OGD would evaluate active ingredient sameness for glatiramer acetate injection during the ordinary course of review and would only approve ANDAs that demonstrate active ingredient sameness and meet the other requirements for approval.

As early as 2009, several ANDA sponsors provided preliminary data for several “glatiramer-like” products that were synthesized under various process conditions and that were not under consideration as ANDA products, but rather were used as negative controls for products under review. These negative control products had the same overall physicochemical characteristics (e.g., molecular weight distribution and amino acid composition) as the RLD, but had different distributions of copolymer sequences, as assessed by ANDA applicants by using structural signatures of polymerization and depolymerization as described above and comparing these structural signatures to the RLD. For example, the differences in these sequences are reflected in the differences in the structural signatures for polymerization kinetics and are attributed to the varying kinetics used in the manufacture of each of these “glatiramer-like” products.⁹² Thus, OGD’s consideration of products that are “like” but not the same as glatiramer acetate injection has only confirmed that the sameness criteria are sufficient to establish active ingredient sameness because of their ability to detect slight differences in the active ingredient.

FDA’s Approach Is Consistent With Other Agency Decisions. As a general matter, FDA makes active ingredient sameness determinations for each drug on a case-by-case basis and our finding

⁸⁹ First Citizen Petition at 16; Second Citizen Petition at 15, 24, 26; Third Citizen Petition at 4, 25; Fourth Citizen Petition at 26; Sixth Citizen Petition at 19.

⁹⁰ First Citizen Petition *supra* note 2 at 15, 33; Sixth Citizen Petition at 19.

⁹¹ See, e.g., Second Citizen Petition at 26, Fourth Citizen Petition at 31, 33; Sixth Citizen Petition at 31; Seventh Citizen Petition at 11-17; Nov. 13, 2014, Supplement to the Seventh Citizen Petition at 4, 12, Appendix 1.

⁹² Similar arguments are asserted by Teva (Sixth Citizen Petition at 21).

of active ingredient sameness is based on relevant scientific information and is specific to each active ingredient. Nonetheless, Teva claims that the agency's decisions as to active ingredient sameness for other complex drug products require "substantial certainty regarding the active ingredient's composition . . . a clear understanding of the RLD's mechanism of action and reli[ance] on knowledge gained from past clinical experience to rule out the possibility that [any] differences are clinically relevant."⁹³ Although FDA does rely on knowledge gained from the Agency's past practice in connection with its determinations, it does so when applicable and when such reliance is appropriate, given other relevant factors and considerations.

For example, Teva refers to FDA's 1997 determination that a synthetically-derived generic conjugated estrogens product could not be approved as an ANDA using Premarin (a naturally-sourced conjugated estrogens product) as the RLD.⁹⁴ In that decision, FDA determined that "because the reference listed drug Premarin is not adequately characterized at this time, the active ingredients of Premarin cannot now be definitively identified."⁹⁵ FDA concluded that "[a]ny synthetic generic conjugated estrogens application based upon Premarin as the reference listed drug is not to be approved until the active ingredients of Premarin have been sufficiently well defined to permit an ANDA applicant to establish that a synthetic generic form of Premarin has the same active ingredients as Premarin."⁹⁶

Teva's reliance on the Premarin example is misplaced. Unlike Copaxone, Premarin is naturally-sourced from the urine of pregnant mares and the Agency's determination related to the ability of a synthetically-derived product to be approved as an ANDA when the RLD and all of its clinically meaningful components had not been adequately characterized.⁹⁷ In essence, in the case of Premarin, the Agency found that a synthetic manufacturing method could not be substituted for a naturally-derived source when there were not adequate assurances that all clinically meaningful components of the naturally-sourced materials would be reproduced in a synthetically-derived version. In this case, by contrast, Copaxone is synthetically derived, with an adequate control of the starting materials including NCA-amino acids and initiator, as described above. The sameness criteria described above would require that a generic glatiramer acetate be synthesized using the same (or equivalent) starting materials and initiator.⁹⁸ The

⁹³ Second Citizen Petition at 7-8.

⁹⁴ For example, First Citizen Petition at 20, Third Citizen Petition at 8-9; Sixth Citizen Petition at 28-29.

⁹⁵ Memorandum from Woodcock, J dated May 5, 1997 re: Approvability of a Synthetic Generic Version of Premarin, at 1.

⁹⁶ Id.

⁹⁷ Id.

⁹⁸ Teva characterizes the source material of Copaxone not as its constituent NCA- amino acids, but rather as the polypeptide mixture resulting from the polymerization process (prior to deprotection/depolymerization) (e.g., Third Citizen Petition at 14; Sixth Citizen Petition at 33-34). We disagree with this characterization because, among other considerations, as described above, the initiation and polymerization steps in the synthesis process are distinctive and fundamental steps in the manufacture of Copaxone. Teva also asserts that it carefully controls the ratio and purity of the amino acid starting materials. (Sixth Citizen Petition at 33) As described further above, the sameness criteria described in this memorandum require equivalence of fundamental reaction schemes, coupled with the

Agency's concerns regarding the characterization of Premarin do not, as asserted by Teva, apply to Copaxone. Furthermore, OGD has determined that Copaxone's glatiramer acetate has been adequately characterized for purposes of approving an ANDA for glatiramer acetate injection.

For similar reasons, Teva's citation to an FDA determination relating to another naturally-derived RLD, Pergonal (menotropins), is misplaced. Pergonal is derived from the urine of postmenopausal women,⁹⁹ where synthesis occurs in vivo. In 1997, FDA found the "same active ingredient" for a proposed generic version of Pergonal, despite naturally occurring variations (microheterogeneity) in the products' carbohydrate side chains.¹⁰⁰ Teva claims that two findings "were crucial to the Agency's sameness determination": (1) the ANDA applicant had established that the protein backbones and specific amino acid sequences in the RLD and proposed ANDA product were identical, that the two products were equally potent, and that the two products showed the same degree of batch-to-batch uniformity as measured by the same bioassays and specifications, and (2) FDA had long-term experience with another menotropins product (Humegon) that showed the same kinds of microheterogeneity as the proposed ANDA product, and clinical trials and published literature "demonstrated no differences in safety and efficacy" between Pergonal and Humegon.¹⁰¹ These specific findings are not relevant here because Pergonal, a naturally-derived product, raised different considerations than Copaxone, a synthetically-derived product. For Copaxone, an ANDA would be expected to have equivalent batch-to-batch uniformity as the RLD; demonstrating that equivalence is part of the active ingredient sameness criteria that are unique to Copaxone, such as equivalent structural signatures for polymerization and depolymerization. Further, for Pergonal, FDA was aware that differences existed but concluded that they did not matter. For Copaxone, by contrast, a generic product meeting the four criteria will have all of the same components as Copaxone (within the context of its variability).

Nor are two additional FDA decisions involving naturally-derived products relevant here. Teva cites FDA's determination that the complexity of certain naturally-derived pancreatic enzyme products (exocrine) renders currently available chemical and bioanalytical tools likely unable to demonstrate active ingredient sameness, and the Agency's conclusion that the current lack of complete characterization makes it impossible to determine whether two hyaluronidase products are the same.¹⁰² Like the Pergonal example cited above, the specific findings regarding exocrine and hyalurodinase are inapplicable here because they were specific to those active ingredients and involved different considerations by the Agency; for example, the Agency's reasoning relied

remaining three criteria, which further confirm both sameness and equivalence of the underlying chemical synthesis, including the ratio and purity of the starting materials.

⁹⁹ *Serono*, 158 F.3d at 1316.

¹⁰⁰ Second Citizen Petition at 19 (citing Letter from Woodcock, J., Docket No. 92-0487, at 10-13 (June 17, 1997)).

¹⁰¹ *Id.*

¹⁰² Second Citizen Petition at 20 (citing Letter from Galson, S., docket no. 2005P-0134/CP1 (Oct. 25, 2005) ("Hyaluronidase Petition Response"), and Guidance for Industry: Exocrine Pancreatic Insufficiency Drug Products – Submitting NDAs (Apr. 2006) ("Exocrine Guidance").

upon the natural source of those drug products.¹⁰³ As noted above, the Agency has determined that Copaxone’s glatiramer acetate has been adequately characterized for purposes of demonstrating active ingredient sameness for ANDA approval.

Teva does not and cannot identify similarities between glatiramer acetate injection and these other drug products (Pergonal, exocrine, and hyaluronidase) that would make FDA’s active ingredient sameness determinations as to those products relevant to glatiramer acetate injection in the way that Teva asserts. As explained above, this memorandum sets forth an approach to determining active ingredient sameness that is based upon the unique chemical properties of glatiramer acetate injection and, therefore, is specific to this drug product.

Copaxone’s Activity. In addition, Teva asserts that Copaxone’s mechanism of action is akin to other product types and glatiramer acetate should be considered consistent with FDA’s scientific evaluations of those product types. For example, Teva asserts that Copaxone has therapeutic vaccine-like activity and impacts anti-glatiramer acetate-specific antibodies.¹⁰⁴ Nonetheless, a complete understanding of glatiramer acetate’s mechanism of action is not a necessary consideration in a determination of active ingredient sameness.¹⁰⁵ There are many approved drug products whose mechanism of action is uncertain, but this has not precluded approval of ANDAs for those products.¹⁰⁶

B. Bioequivalence

Glatiramer Acetate Injection Is a Parenteral Solution. Glatiramer acetate injection is a parenteral solution. Therefore, if active ingredient sameness is established based upon the above criteria by an ANDA applicant and the drug product is qualitatively and quantitatively the same in terms of active and inactive ingredients, then bioequivalence would be self-evident and any

¹⁰³ See Hyaluronidase Petition Response, at 5 (“[T]he Agency cannot determine the specific enzyme or enzymes contained in any naturally sourced hyaluronidase product”); Exocrine Guidance, at 1 (noting that the relevant enzymes are contained in ingredients “which are of animal origin”).

¹⁰⁴ For example, First Citizen Petition at 10, 11; Second Citizen Petition at 9, 16; Third Citizen Petition at 24, Fourth Citizen Petition at 4, 7, 26-28; Sixth Citizen Petition at 9, 38.

¹⁰⁵ Demonstrating that a proposed drug product has the same mechanism of action is not a criterion for showing active ingredient sameness, including as described in section 505(j)(2)(A) of the Act or 21 CFR 314.92(a)(1). Several of Teva’s assertions in support of the company’s challenge to generic glatiramer acetate injection relate to the limitations of understanding of Copaxone’s mechanism of action and several theoretical mechanisms of action (e.g., First Citizen Petition at 7, 28, 29; Second Citizen Petition at 3-4, 13-15, 17, 22-23; Third Citizen Petition at 3-4; Fourth Citizen Petition at 7, 8-9, 30-31; Sixth Citizen Petition at 25, 31, 32-33, 47 and the Jan. 27, 2014 Supplement to the Sixth Citizen Petition at 10). Similar assertions are made in the Peptimmune Citizen Petition, at 3, 6-7, 9. These limitations in understanding do not preclude a finding of active ingredient sameness, as further described above.

¹⁰⁶ For example FDA has approved generic versions of valproic acid and propofol. We note that these ANDA products have been approved despite poorly understood mechanisms of action.

requirement to submit in vivo evidence of bioequivalence may be waived under 21 CFR 320.22(b) (commonly referred to as a “biowaiver”).^{107, 108}

In its fourth and sixth citizen petitions, Teva asserted that an in vivo bioequivalence waiver is inappropriate for glatiramer acetate injection because of colloidal characteristics of Copaxone.¹⁰⁹ Teva cited FDA’s recommendation for in vivo bioequivalence studies for Ferrlecit (sodium ferric gluconate injection)¹¹⁰ and results of Dynamic Light Scattering (DLS) and Atomic Force Microscopy (AFM) evaluations of glatiramer acetate and a summary of results of ultracentrifugation/ reconstitution, cryogenic temperature transmission electron microscopy (Cryo-TEM), and zeta potential testing in support of these assertions.¹¹¹

A Biowaiver Is Appropriate Because Glatiramer Acetate Injection Is a Solution. As noted above, a biowaiver is appropriate for a glatiramer acetate injection that is a parenteral solution and qualitatively and quantitatively the same in terms of active and inactive ingredients as Copaxone because bioequivalence is considered self-evident under 21 CFR 320.22(b).¹¹² The assertions made by Teva regarding Copaxone’s colloidal properties are not inconsistent with its characterization as a solution because solutions can have colloidal properties. For example, even if glatiramer acetate exists as nano-sized complexes of varying sizes in Copaxone (based on available dynamic light scattering (DLS), as asserted by Teva), this does not change the

¹⁰⁷ We note that the proposed rule regarding biowaivers included the following explanation: “The agency does not believe Congress intended that unnecessary human research be conducted in cases where an applicant could demonstrate that a product is inherently bioequivalent to another product and therefore meets the statutory standard of bioequivalence.” 54 FR 28872 at 28883 (July 10, 1989).

¹⁰⁸ In its Fourth Citizen Petition (at 20-21), Teva asserts that comparative in vivo bioequivalence studies with clinical endpoints should be required because, among other things, FDA refused to approve an sNDA for a modified formulation of Copaxone that contained the same active ingredient in a higher concentration and lower volume. See also Sixth Citizen Petition at 52-53. Teva contends that FDA explained that it could not approve the sNDA without clinical efficacy studies because “[t]he uncertainty about the glatiramer acetate mechanism of action, and the fact that some of the effect may be related to the activation of lymphocytes in the periphery, raise questions about a possible impact of a higher concentration/lower volume formulation on the safety and efficacy of the product.” Teva contends that “[i]f FDA cannot be sure that the absence of 0.5 mL of water will not affect safety or efficacy without requiring clinical studies, it cannot possibly determine that a purported generic product with an active ingredient that invariably will differ from the glatiramer acetate in Copaxone will have the same safety and efficacy profile without requiring comparative *in vivo* studies with meaningful clinical endpoints.” Teva’s attempt to draw an analogy between the approval of an ANDA for glatiramer acetate injection and FDA’s action on Teva’s sNDA is flawed because – unlike a proposed generic product that satisfies the conditions for a biowaiver – the modified formulation of Copaxone, which changed the strength of the product, was not qualitatively and quantitatively the same as the original formulation.

¹⁰⁹ For example, Fourth Citizen Petition *supra* note 2 at 4 – 9, 12; Sixth Citizen Petition at 42 – 53.

¹¹⁰ Fourth Citizen Petition at 13.

¹¹¹ Fourth Citizen Petition *supra* note 2 at 19 – 20; Sixth Citizen Petition at 45.

¹¹² We note that the glatiramer acetate injection proposed by Sandoz in its ANDA is qualitatively and quantitatively the same in terms of active and inactive ingredients as Copaxone and, as discussed in the relevant OGD/OPQ review documents for its ANDA, Sandoz’s proposed product was granted a biowaiver.

fundamental premise that glatiramer acetate is fully dissolved in aqueous solution and exists as a solution, like other typical parenteral solutions for which FDA has granted biowaivers.

Light scattering methods are typically used to characterize colloidal systems. The intensity of the scattered light (I_s) increases exponentially to the sixth power with the size (hydrodynamic diameter, d_h) of the scattering center, regardless of whether the scattering centers are fully dissolved in true solutions or exist as phase disperse or undissolved species in colloidal dispersions. The scattering intensity of glatiramer acetate is consistent with a scattering center having a diameter on the order of 1 to 2 nm, however such scattering is simply a reflection of the size of the polymeric species (on the order of 5-9 KDa) that comprise glatiramer acetate, and does not separately suggest, as has been contended by Teva,¹¹³ dispersed or “undissolved” glatiramer acetate particles.

For example, oxytocin¹¹⁴ exhibits light scattering, and this property has been used to determine the particle size distribution, molecular weight and other physical characteristics. We note that oxytocin exhibits a scattering diameter > 1 nm, typical of a colloid.¹¹⁵ Similarly, hetastarch, a plasma volume expander, also scatters light and is considered a colloid.^{116, 117} Regardless of the designation or characteristic of these products being colloids, these products are solutions and waivers of in-vivo bioequivalence studies have been granted for these products.¹¹⁸

There are several lines of evidence that demonstrate that, as long as glatiramer acetate injection is stored under Copaxone’s labeled storage conditions, glatiramer acetate is fully dissolved as in

¹¹³ Sixth Citizen Petition at 8, 30-31.

¹¹⁴ Hawe A, Hulse WL, Jiskoot W, Forbes RT, Taylor dispersion analysis compared to dynamic light scattering for the size analysis of therapeutic peptides and proteins and their aggregates. *Pharmaceutical Research* 2011; 28:2302-2310.

¹¹⁵ Id.

¹¹⁶ Lederer K, Huber C, Dunky M, Fink JK, Ferber HP, Nitsch E, Studies on hydroxyethyl s part 1 molecular characterization by size exclusion chromatography coupled with low-angle laser light scattering. *Arzneimittel-Forschung* 1985; 35(3):610-614.

¹¹⁷ Hulse JD, Yacobim Hetastarch A. An overview of the colloid and its metabolism, *Drug Intell Clin Pharm* 1983;17(5):334-41.

¹¹⁸ Teva makes an analogous contention using zeta potential testing of Copaxone to demonstrate its colloidal properties. (Sixth Citizen Petition at 45 (citing Bawa Declaration, Ex. 26) Zeta potential testing is a measurement of electrokinetic potential over the surface of an object when exposed to a fluid and is often a key indicator of the stability of a colloidal system. See, e.g., “IUPAC. Compendium of Chemical Terminology”, 2nd ed., compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). See also Derjaguin B; Landau L (1941) Theory of the stability of strongly charged lyophobic sols and of the adhesion of strongly charged particles in solutions of electrolytes, *Acta Physico Chemica URSS* 14, 633 and W. B. Russel, D. A. Saville, W. R. Schowalter (1989) *Colloidal Dispersions*, Cambridge University Press, UK. Teva’s assertions on this point do not impact OGD’s assessment of glatiramer acetate injection being a solution eligible for a biowaiver because, in a similar vein as described above with respect to the light scattering arguments, they are consistent with OGD’s determination.

a true solution with no evidence of suspended glatiramer particles, such as would be contained in a colloidal dispersion.¹¹⁹

First, ultrafiltration studies reviewed by OGD/OPQ in connection with review of Sandoz's ANDA for glatiramer acetate injection show that glatiramer acetate has the same hydrodynamic diameter before and after ultrafiltration, which is consistent with the absence of undissolved glatiramer acetate particles. This is in contrast to iron dextran, which contains suspended undissolved nanoparticulate iron particles and shows significant differences in hydrodynamic diameter following ultrafiltration due to the retention of the nanoparticulate iron dextran (which exists as a colloidal dispersion). However, we note that, if glatiramer acetate injection is placed under stressed conditions outside approved Copaxone's labeled storage conditions, it can form irreversible suspended high molecular weight particles that, like iron dextran, will be retained by ultrafiltration. Conversely, evaluation of glatiramer acetate injection stored under Copaxone's labeled storage conditions using multiple techniques to evaluate potential aggregates including analytical ultracentrifugation and asymmetric field flow fractionation do not show evidence of aggregates. Therefore, provided glatiramer acetate injection is stored under Copaxone's labeled storage conditions, it is fully dissolved as in a true solution.

Second, freezing point depression is a colligative property of solutions, where the freezing point depression is a function of the molar concentration of the solute. By varying the concentration of glatiramer acetate between 0 milligrams (mg)/milliliter (mL) to 50 mg/mL a linear relationship was observed¹²⁰ between the glatiramer acetate concentration and freezing point depression, indicating that across these concentrations (including the concentration of 20 mg/mL concentration of the proposed generic glatiramer acetate injection), glatiramer acetate is completely dissolved in solution. Conversely, a non-linear relationship would indicate incomplete solubilization.

Therefore, the above results demonstrate that, provided glatiramer acetate injection is stored under Copaxone's labeled storage conditions, it is fully dissolved as in a true solution and does not show evidence of suspended or aggregated glatiramer acetate particles present as a colloid. As glatiramer acetate injection is a true solution, even if it has light scattering properties, like any other parenteral solution that is qualitatively and quantitatively the same in terms of active and inactive ingredients, it is eligible for a biowaiver, contrary to Teva's assertions.^{121, 122}

¹¹⁹ Teva makes certain assertions that Copaxone would be more properly classified as a suspension rather than a solution. (See, e.g., Sixth Citizen Petition at 45-46). For the reasons described below, we disagree.

¹²⁰ This observation was based on our review of information submitted in connection with review of Sandoz's ANDA for glatiramer acetate injection.

¹²¹ E.g., Fourth Citizen Petition at 12, Sixth Citizen Petition at 45-47. In Sixth Citizen Petition at 45, Teva claims "*Copaxone constituents can be separated into layers by ultracentrifugation and then easily reconstituted, indicating that Copaxone is a lyophilic colloidal suspension ...*". We disagree with this claim. Based upon our analysis of the data provided by Teva in the petition, we believe this change was induced by the strong centrifugal force and prolonged treatment time (530,000g over 24 hours), and the resulting association complexes in the segregated layer do not exist in the untreated sample. Therefore, Teva's ultracentrifugation data do not support its claim that Copaxone is a lyophilic colloidal suspension. On the other hand, the fact that the reconstituted solution after

Ferrlecit (sodium ferric gluconate injection) Is Distinguishable From Glatiramer Acetate Injection. Ferrlecit is similar in many respects to iron dextran, as previously discussed, as it contains undissolved suspended nanoparticulate iron particles and, as such, exists as a colloidal dispersion and is not a true solution, unlike Copaxone. Therefore any parallels that Teva attempts to draw between Ferrlecit and glatiramer acetate injection are not applicable.

Pharmacokinetic, Pharmacodynamic, or Other Comparative Bioequivalence Studies Not Required. Among Teva's assertions in its Citizen Petitions are arguments connected to Copaxone's unknown mechanisms of action, suggesting potential local, injection site activity of the drug, and a lack of correlation between pharmacokinetics and drug efficacy.¹²³ Teva also contends that pharmacodynamic parameters such as the development of anti-glatiramer acetate antibodies or the stimulation of peripheral blood lymphocytes have not been validated to serve as markers of bioavailability and bioequivalence.¹²⁴ Finally, Teva asserts that clinical endpoint studies would be required to establish bioequivalence.¹²⁵ However, as noted above, glatiramer acetate injection is a parenteral solution and, if the criteria set forth in 21 CFR 320.22(b) are satisfied, a waiver of in vivo bioequivalence studies would be appropriate and would obviate the need for pharmacokinetic studies, pharmacodynamic studies, or other clinical endpoint studies because bioequivalence would be self-evident. If an ANDA meets the standards for a biowaiver, OGD concludes that such a showing will be adequate to demonstrate bioequivalence between a generic glatiramer acetate injection and Copaxone.

ultracentrifugation resembles the physical characteristics of the solution before the treatment suggests that glatiramer acetate injection is thermodynamically stable as a true solution.

¹²² Teva contends that even if a glatiramer acetate injection is a solution eligible for a biowaiver, FDA should still require in vivo bioequivalence studies under 21 CFR 320.22(f). (See Fourth Citizen Petition at 13; Sixth Citizen Petition at 46-48.) Where a proposed generic glatiramer acetate injection is qualitatively and quantitatively the same in terms of active and inactive ingredients as Copaxone, we do not expect to find "good cause" to require evidence of in vivo bioequivalence, nor do we expect to find "any difference between the drug product and the listed drug [that] may affect the . . . bioequivalence of the drug product." 21 CFR 320.22(f). As discussed above, the criteria set forth in this memorandum for active ingredient sameness ensure that a proposed generic glatiramer acetate injection falls within the range of Copaxone's batch-to-batch variability.

¹²³ E.g., First Citizen Petition, at 7, 8, 25, 29-30; Third Citizen Petition at 5; Fourth Citizen Petition at 4, 9, 13-14, 15, 16-17; Sixth Citizen Petition at 49. Similar arguments are made in the Peptimmune Citizen Petition, at 3, 10, 27.

¹²⁴ E.g., First Citizen Petition at 8, 30-31 Second Citizen Petition at 17; Third Citizen Petition at 20, 21, 22; Fourth Citizen Petition at 10, 17-18; Sixth Citizen Petition at 50, 51, 52. Similar arguments are made in the Peptimmune Citizen Petition, at 28.

¹²⁵ E.g., Fourth Citizen Petition at 19-23; Sixth Citizen Petition at 51, 52. Teva attempts to analogize glatiramer acetate injection to two drug products, sucalfate tablets and rifaximin tablets, for which FDA recommended clinical trials to demonstrate bioequivalence. See ANDA No. 70-848, Response to Consultation re: Biocraft Submission of April 27, 1988 (May 2, 1988) (Fourth Citizen Petition Ex. 19), available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/96/070848.PDF, at 179-80. We note that these examples are inapplicable in this instance because, among other factors, these drugs products are oral tablets acting in the gut, rather than qualitatively and quantitatively equivalent parenteral solutions, like glatiramer acetate injection, for which in vivo bioequivalence may be considered self-evident if the drug product meets the criteria set forth in 21 CFR 320.22(b)(1).

C. Immunogenicity

In its citizen petitions, Teva asserts that FDA should require comparative clinical testing to show that the immunogenicity risks associated with any proposed generic product - including risks associated with switching from Copaxone to a generic product - are no greater than those associated with Copaxone.¹²⁶ Teva has postulated a number of such risks, including immune-complex formation, hypersensitivity, additional autoimmune disorders, general immune suppression, immunotoxicity, and eosinophilia.¹²⁷

As discussed elsewhere in this memorandum, Copaxone has an array of peptide copolymers that can activate the immune system and stimulate an immune response. OGD agrees that a generic glatiramer acetate injection must not elicit a different immune response from Copaxone.¹²⁸ Therefore, it is important that an ANDA applicant demonstrate that its generic glatiramer acetate product has the same active ingredient as Copaxone. The criteria listed previously – equivalence of fundamental reaction scheme, physicochemical properties, structural signatures for polymerization and depolymerization, and results in biological assay with respect to Copaxone – will ensure that a generic glatiramer acetate injection has the same molecular diversity (and active ingredient) as Copaxone.

In addition to active ingredient sameness, we have previously considered whether impurities may affect the immunogenicity of drug products, including in the case of enoxaparin.¹²⁹ In the case of generic glatiramer acetate injection, impurities including aggregates, leachates and process related impurities will be evaluated and their levels will also be rigorously controlled. Aggregation is usually a result of non-specific interactions between molecules to form high molecular weight species. Based on information from the literature, the propensity for aggregation in glatiramer acetate is quite low.¹³⁰ Nonetheless, the formation of irreversible aggregates in glatiramer acetate is possible under highly stressed conditions, outside Copaxone's labeled storage conditions. Thus, aggregates of the glatiramer acetate copolymer are considered potential impurities and are critical to control because they may have a profound effect upon the

¹²⁶ Sixth Citizen Petition, supra note 2 at 23, 37 – 40; Third Citizen Petition at 23 – 25; Fourth Citizen Petition at 25 – 32.

¹²⁷ Third Citizen Petition at 23; Sixth Citizen Petition, supra note 2 at 10, 24 – 25; 37, 38, 39-40.

¹²⁸ Several of Teva's assertions relate to minor variations of sequence between generic glatiramer acetate and the active ingredient in the RLD that could have immunogenic consequences (e.g., Third Citizen Petition at 23, 24, 25; Fourth Citizen Petition at 24-25, 26, 29). For example, Teva asserts that sameness criteria based on "bulk physicochemical characteristics" could present "different antigenic epitopes arising from small changes in the product's primary structure." (Third Citizen Petition at 23.) We note, however, that these assertions conflict with the batch-to-batch variability, or molecular diversity, inherent in Copaxone itself discussed above.

¹²⁹ Lee S, Raw A, Yu L, Lionberger R, Ya N, Verthelyi D, Rosenberg A, Kozlowski S, Webber K, Woodcock J. Scientific considerations in the review and approval of generic enoxaparin in the United States. *Nature Biotechnology* 2013 (31) 220-226.

¹³⁰ Varkony H, Weinstein V, Klinger E, Sterling J, Cooperman H, Komlos T, et al. The glatiramoid class of immunomodulator drugs. *Expert opinion on pharmacotherapy*. 2009;10(4):657-68.

immunogenicity of the drug product and may produce antigenic responses.¹³¹ The levels of peptide copolymer aggregates will be assessed by using size exclusion chromatography in conjunction with orthogonal techniques such as analytical ultracentrifugation and field flow fractionation.^{132, 133} Because the aggregates of glatiramer acetates are undesirable in the drug product due to safety concerns, ANDA applicants need to ensure that the amount of aggregation in the generic product will be no more than in the RLD under stability testing conditions.

Provided that active ingredient sameness and the other ANDA approval requirements are met, the generic product will be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in its labeling and thus can be substituted for the RLD.¹³⁴ As noted above, the underlying premise of the ANDA approval requirements is that a generic drug product that meets the approval requirements can be substituted for the RLD with the full expectation that it will have the same clinical effect and safety profile.¹³⁵ Accordingly, we expect that any glatiramer acetate injection that meets the requirements for ANDA approval will not be associated with greater immunogenicity risks than Copaxone.

E. Gene Expression

In its Sixth, Seventh, and Eighth Petitions, Teva compared the effects of Copaxone to the effects of other glatiramer acetate (or glatiramer acetate-like) injection products (none approved by FDA) on gene expression in mouse splenocytes or human monocytes. The gene expression data were used in an effort to compare the pharmacological effects of generic drug products and Copaxone. In the Sixth Petition, Teva reported the results of (1) a study analyzing gene expression in mouse splenocytes activated with Copaxone, the unapproved product TV-5010 (produced by Teva for research and not approved in any jurisdiction), or the foreign product Glatimer (Natco Pharma, India),¹³⁶ and (2) a study analyzing gene expression in mouse splenocytes activated with a foreign product or active pharmaceutical ingredient (including :

¹³¹ Rosenberg AS. Effects of protein aggregates: an immunologic perspective. *AAPS Journal*, 2006 (8) 501-507.

¹³² Liu J, Andya JD, Shire SJ. A critical review of analytical ultracentrifugation and field flow fractionation methods for measuring protein aggregation. *AAPS Journal*, 2006; 8: E580-E589.

¹³³ We note that, as discussed in the relevant OGD/OPQ review documents for its ANDA, Sandoz's proposed product was assessed on these grounds.

¹³⁴ The ANDA approval standards for glatiramer acetate injection that are set forth in this response, including those relating to active ingredient sameness and impurities, reflect extensive and careful consideration by the Agency. FDA has concluded that the clinical trials that Teva suggests are not necessary to establish active ingredient sameness or for any other purpose because, among other reasons, they are less sensitive than the four criteria at detecting differences between products. Teva's analysis of results from the GATE clinical trial comparing Copaxone to a Synthon product (GTR) and placebo does not affect our conclusions about active ingredient sameness because the appropriate methodology for any such clinical trial is not relevant. See Nov. 13, 2014 Supplement to the Sixth Petition, at 12-14 & Appendix 2; Eighth Citizen Petition at 2, 4.

¹³⁵ See Orange Book, 35th ed., at vii.

¹³⁶ Sixth Petition at 10.

Escadra (Argentina), Probioglat (Mexico), and Hangzhou (China)).¹³⁷ In the Seventh Petition, Teva provided a more thorough discussion of its mouse splenocyte study, and also reported the results of experiments in the human monocyte (THP-1) line comparing Copaxone with other glatiramer acetate or glatiramer acetate-like products, including Probioglat.¹³⁸ In a supplement to the Seventh Petition, Teva provided an initial report of preliminary findings from gene expression studies in the THP-1 cell line conducted on Polimunol (Synthon, Argentina).¹³⁹ In the Eighth Petition, Teva reported new data including the results of gene expression studies in mouse splenocytes and the THP-1 cell line conducted to compare Polimunol with Copaxone.¹⁴⁰ Teva claims that these studies identified differences between Copaxone and the comparators that “warrant further studies.”¹⁴¹

After careful consideration of Teva’s data submitted in its Sixth Petition, the Agency determined that the basic experimental design was not appropriate for product comparisons, and that the results generated from the study would be problematic if used as a basis for considering the active ingredient sameness of a generic product versus a RLD.¹⁴² Specifically, we concluded that the mouse splenocyte studies were poorly designed, contained a high level of residual batch bias, and used non-standard statistical criteria for assessing the presence of differentially expressed genes. When FDA reanalyzed the microarray data from one Teva study using industry standard practices and criteria, Copaxone and the comparator (Natco) product were found to have very similar effects on the efficacy-related pathways proposed for glatiramer acetate’s mechanism of action.

FDA identified similar methodological flaws in Teva’s gene expression data submitted in its Seventh Petition. Because that petition reported on the same mouse splenocyte studies that FDA had evaluated and found deficient in connection with the Sixth Petition, FDA concluded that any arguments concerning differences between Copaxone and comparator products based on the Teva’s analysis of the mouse splenocyte data could not be supported. With respect to Teva’s gene expression study in “human monocytes,” FDA found that it was not conducted with normal or patient human monocytes but rather with a transformed human cell line, THP-1. Although the THP-1 cell line is a widely used research model that retains a subset of characteristics of primary

¹³⁷ Sixth Petition at 18.

¹³⁸ Seventh Petition at 19-46.

¹³⁹ Nov. 13, 2014 Supplement to Seventh Petition at 31-38.

¹⁴⁰ Eighth Petition at 41-43.

¹⁴¹ Seventh Petition at 4; Eighth Petition at 5.

¹⁴² We note that regarding the use of these kinds of studies generally in connection with a determination of active ingredient sameness, the Agency determined that, based on current scientific understanding, microarray-derived gene expression data alone will be inconclusive, but could be used as part of the total evidence presented in support of an assertion, not as standalone evidence; provided that certain key requirements for assessing product quality, data quality and biological relevance can be identified as critical to ensuring that microarray data are reliably collected, analyzed and interpreted. We also conclude that while gene expression data could be used as supportive evidence of an active ingredient sameness determination, it is not necessary in this instance because the active ingredient sameness criteria described above are sufficient in that the criteria are robust and provide overlapping and confirmatory evidence of active ingredient sameness.

human monocytes, FDA concluded that Teva had not adequately justified how its gene expression studies alone in this cell line can be considered to adequately report on the complex therapeutic effect of glatiramer acetate in MS patients. In particular, Teva provided no evidence showing that the responses of THP-1 cells represented the response expected in normal human monocytes or that this experimental model reliably reproduced known therapeutic responses to glatiramer acetate. For example, the data in the Seventh Petition report that the maximal gene array response of THP-1 cells to glatiramer acetate was observed at 6 hours and was nearly absent at 24 hours. This contrasts significantly with the data from a published study with peripheral blood mononuclear cells (PBMC) from MS patients which showed the maximal response was not seen until 24 hours.¹⁴³ FDA concluded that the Teva study designs and gene expression data were sufficiently flawed such that it is impossible to make any determinations about therapeutic mechanisms of action of glatiramer acetate in MS patients and their genetic components, and that Teva's methods and data did not convincingly demonstrate any differences in gene expression among Copaxone and other glatiramer acetate or glatiramer acetate-like products.

The November 13, 2014 Supplement to the Seventh Petition also described a study described using the human acute monocytic leukemia cell line THP-1, which FDA had concluded was not a validated system and could not be interpreted as having any predictive value for human clinical responses. Moreover, in analyzing that study, Teva used non-standard statistical criteria for assessing the presence of differentially expressed genes.

FDA concluded that the study design described in the Eighth Petition overstated treatment differences by artificially minimizing biological variability, and that Teva had reported the data in a way that maximized small effects between treatments that may not be clinically significant. FDA further determined that the THP-1 studies reported in the Eighth Petition suffer from the same fatal design flaws as the experiments reported in the Seventh Petition and the November 13, 2014 Supplement to the Seventh Petition.

After reviewing all of the gene array experiments and resulting data submitted by Teva, FDA concluded that they did not provide useful information relevant to the issue of the approvability of an ANDA referencing Copaxone.

¹⁴³ Hong J, Zang YCQ, Hutton G, Rivera VM, Zhang JZ. (2004) Gene expression profiling of relevant biomarkers for treatment evaluation in multiple sclerosis. *J Neuroimmunol* 152, 126-139.




Memorandum

Date April 09, 2015

From Ruth Moore, PhD.
Compliance Officer
Division of Inspectional Assessment (DIA)
Office of Process and Facilities (OPF)
CDER, Office of Pharmaceutical Quality (OPQ)

Subject Confirmation of Non-Concurrence with (b) (4) District Office ((b) (4) -DO)
Withhold Recommendation for: ANDA 90218 (GLATIRAMER ACETATE Injection)

Thru Zihao Peter Qiu, PhD.  4/9/2015
Branch Chief
Division of Inspectional Assessment (DIA)
Office of Process and Facilities (OPF)
CDER, Office of Pharmaceutical Quality (OPQ)

To Sau (Larry) Lee, PhD. (Acting) Associate Director for Science, OPQ
Andre Raw, PhD., Acting Senior Scientific and Policy Advisor, OLDP/OPQ
Kshitij (Kris) Patkar, PhD., Review Chemist, OPF/OPQ, Reviewer for ANDA 90218
Jing Li, PhD., Review Chemist, OPF/OPQ, Reviewer for ANDA 90218
Simon Eng, PhD., Regulatory Project Manager for ANDA 90218

Sponsor: Sandoz Inc.
506 Carnegie Center Suite 400
Princeton, NJ 08540

Control Testing Laboratory:



This memorandum confirms the Office of Pharmaceutical Quality's (OPQ) non-concurrence with the (b) (4) District Office ((b) (4) -DO) withhold recommendation for ANDA 90218. This case was originally handled by the Office of Manufacturing and Product Quality (OMPQ) in the Office of Compliance (OC). However, with the recent reorganization of CDER, oversight of this case has been migrated to OPQ.

ANDA 90218

In a memorandum dated August 18, 2014, OMPQ explained that it did not concur with (b) (4) DO's withhold recommendation for ANDA 90218 under the condition that the firm provide certain information. Specifically, the memorandum stated that the Information Request that the Office of Pharmaceutical Science (OPS) would send to address any analytical or other deficiencies would include the following request from CDER/OC:

As part of CDER's review of the withhold recommendation from the district, please provide a signed statement that once the stability methods/testing matrix has been finalized in correspondence with OPS, that all methods will be verified at the facilities that will be performing those tests.

The memorandum stated that CDER/OC reserved the right to reverse its decision not to concur with (b) (4) DO's withhold recommendation if the firm did not provide the requested signed statement, or if its response to OPS regarding stability testing was found to be inadequate.

OPS sent the Information Request to Sandoz, Inc. (Sandoz) on August 19, 2014. Sandoz provided the requested signed statement to FDA on October 01, 2014. The firm provided a signed statement of Stability Commitment. OPQ has determined that Sandoz's response to OPS regarding stability testing is adequate. CDER/OPQ therefore confirms its non-concurrence with (b) (4) DO's withhold recommendation for ANDA 90218. The site is acceptable.

If you have questions, please contact me at 240-402-9988 or ruth.moore@fda.hhs.gov.

Ruth Moore 4/9/2015

Ruth Moore, Ph.D.
Compliance Officer
Division of Inspectional Assessment (DIA)
Office of Process and Facilities (OPF)
CDER, Office of Product Quality (OPQ)

cc:

(b) (4) DO Pre-Approval Manager (PAM), (b) (4)

HFD-323 Shared Drive\cdnas\OCS1\OC_320\HFD-323\Domestic PAI Case Management
CMS Work Activity #: (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SIMON S ENG
04/09/2015



ANDA 090218

**TELECONFERENCE
MEETING MINUTES**

Sandoz Inc.
Attention: Jean Domenico
555 West Midway Blvd
Broomfield, CO 80020

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL, dispensed in 1 mL prefilled syringes.

We also refer to the teleconference between representatives of your firm and the FDA on March 11, 2015. The purpose of the FDA requested teleconference meeting was to request additional information regarding the on-going drug product quality review.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Simon Eng, at (240) 402-8932.

Sincerely,

Simon S. Eng -S

Simon Eng, PharmD
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Digitally signed by Simon S. Eng -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Simon S. Eng -S,
0.9.2342.19200300.100.1.1=1300222917
Date: 2015.03.25 13:03:42 -04'00'

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Post CR Teleconference
Meeting Category: On-going Review
Meeting Date and Time: March 11, 2015 1:30 P.M.

Application Number: 090218
Product Name: Glatiramer Acetate Injection, 20 mg/mL
Sponsor/Applicant Name: Sandoz, Inc.

Meeting Recorder: Simon Eng, PharmD

FDA ATTENDEES

Jing Li, PhD, ANDA Reviewer, OPQ
Kshitij (Kris) Patkar, PhD, ANDA Reviewer, OPQ
Andre Raw, PhD, Senior Science and Policy Advisor, OPQ

SPONSOR ATTENDEES

Attendees from Sandoz:

Jean Domenico, Associate Director, Regulatory Affairs
Anthony Maffia, III, Vice President, Regulatory Affairs
Aleksandr Kravtsov, Global Head Neurology Franchise, Biopharmaceuticals

Attendees from Momenta:

James Anderson, VP Analytical Development
Christine Bell, Senior Director, Analytical Development
John Bishop, SVP Pharmaceutical Sciences
Claire Coleman, Associate Director, Chemical Development
Ian Fier, VP Strategic Product Development, Program Leader
Jon Lansing, Associate Director, Research
Richard Sachleben, Research Fellow, Chemical Development
Carolyn Huntentburg, Vice President, Regulatory Affairs

Teleconference Meeting Minutes

1.0 BACKGROUND

The purpose of the Teleconference is to request additional information regarding the manufacturing process of the drug product.

2.0 DISCUSSION:

The Agency requested meeting with Sandoz/Momenta to request additional information/explanation for the reaction mechanisms involved in the polymerization step of Sandoz/Momenta's Glatiramer Acetate (GA) manufacturing process.

[REDACTED] (b) (4)

Sandoz/Momenta stated that such experiment would not be trivial from technical perspective and no new experiments are necessary to offer further evidence [REDACTED] (b) (4) in polymerization.

Sandoz/Momenta offered their explanation for sufficiency of the data generated in the previous experiments which was provided in the April 06, 2012 submission. Sandoz/Momenta explained the data in the April 06, 2012 submission to justify the sufficiency of the experiments to

[REDACTED] (b) (4)

The Agency agreed to take a look at the experimental data in the April 06, 2012 submission as well as the data on the kinetics on model systems and mathematical modeling data for polymerization kinetics.

Teleconference Meeting Minutes

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
None	FDA	N/A
Will submit requested information	Sponsor	As soon as possible

5.0 ATTACHMENTS AND HANDOUTS

None



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 090218

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sandoz Inc.
2655 West Midway Boulevard
P.O. Box 446
Broomfield, CO 80038-0446

ATTENTION: Jean Domenico
Associate Director, Regulatory Affairs

Dear Ms. Domenico:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received October 1, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL.

We also refer to:

- Our February 20, 2015, email requesting that you re-submit your request for proprietary name, Glatopa
- Your correspondence, dated and received February 20, 2015, requesting review of your proposed proprietary name, Glatopa

We have completed our review of the proposed proprietary name, Glatopa and have concluded that it is acceptable.

If your application receives a complete response and six months or more has elapsed between the date you were notified of our decision on your proposed proprietary name and the date you respond to the application deficiencies, please submit a new request for review of your proposed proprietary name when you respond to the application deficiencies. See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

If any of the proposed product characteristics as stated in your February 20, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Aaron Sigler, Regulatory Project Manager in the Office of Generic Drugs, at 240-402-8786.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/26/2015

Wright, Kevin

From: Hansen, Lara <lara.hansen@sandoz.com>
Sent: Friday, February 20, 2015 3:08 PM
To: Wright, Kevin; McCullough, Kim
Cc: Domenico, Jean
Subject: RE: Sandoz ANDA 090218 - Submission

Thank you Kevin,

I would like to confirm that the submission was successfully submitted through the gateway.

Thanks again,
Lara

Lara Hansen

Sandoz Inc.
Regulatory Affairs
Broomfield, CO USA
1-303-438-4353

lara.hansen@sandoz.com
www.sandoz.com

From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Friday, February 20, 2015 12:22 PM
To: Hansen, Lara; McCullough, Kim
Cc: Domenico, Jean
Subject: RE: Sandoz ANDA 090218 - Submission

Hi Lara,

Thank you for the prompt response. I am confirming receipt of your email. I look forward to receiving your eCTD submission.

From: Hansen, Lara [<mailto:lara.hansen@sandoz.com>]
Sent: Friday, February 20, 2015 1:20 PM
To: Wright, Kevin; McCullough, Kim
Cc: Domenico, Jean
Subject: Sandoz ANDA 090218 - Submission

Hi Kevin,

As requested, we are working on our eCTD submission and will file through the gateway shortly. Attached is an electronic copy of the cover letter and 356h for your reference.

Please let us know if there is anything else that you need.

Thank you,
Lara

Lara Hansen

Sandoz Inc.
Regulatory Affairs
Broomfield, CO USA
1-303-438-4353

lara.hansen@sandoz.com
www.sandoz.com

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/s/

KEVIN WRIGHT
02/24/2015



ANDA 090218

**TELECONFERENCE
MEETING MINUTES**

Sandoz Inc.
Attention: Jean Domenico
555 West Midway Blvd
Broomfield, CO 80020

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL, dispensed in 1 mL prefilled syringes.

We also refer to the teleconference between representatives of your firm and the FDA on November 14, 2014. The purpose of the requested teleconference meeting was to discuss deficiencies noted in the ECD letter dated November 13, 2014.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Simon Eng, at (240) 402-8932.

Sincerely,

{See appended electronic signature page}

Product Quality Regulatory Project Manager
Division of Chemistry
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Post ECD Teleconference
Meeting Category: On-going Review
Meeting Date and Time: November 14, 2014 3:00 P.M.

Application Number: 090218
Product Name: Glatiramer Acetate Injection, 20 mg/mL
Sponsor/Applicant Name: Sandoz, Inc.

Meeting Recorder: Simon Eng, PharmD

FDA ATTENDEES

Sau (Larry) Lee, PhD, Act. Associate Director for Science, OPS
Jing Li, PhD, ANDA Reviewer, OPS
Kshitij (Kris) Patkar, PhD, ANDA Reviewer, OPS
Andre Raw, PhD, Division Director, ANDA Review Division 1, OPS

SPONSOR ATTENDEES

Sandoz Inc. attendees:
Anthony Maffia, Vice President, Regulatory Affairs
Jean Domenico, Associate Director, Regulatory Affairs

Momenta attendees:
Christine Bell – Senior Director Analytical Development
John Bishop – Senior Vice President, Pharmaceutical Sciences
Jon Lansing – Associate Director, Complex Generics, Research
Jennifer Smith – Vice President, Quality
Kristina Storey – Associate Director, Regulatory Affairs

Teleconference Meeting Minutes

1.0 BACKGROUND

The purpose of the Teleconference is to clarify some of the deficiencies listed on the ECD sent to Sandoz yesterday.

2.0 DISCUSSION

A. Deficiencies

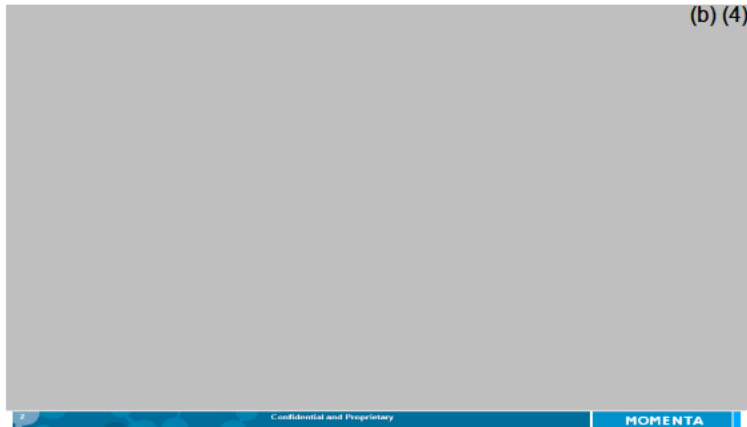
1. [Redacted] (b) (4)

[Redacted] (b) (4)

Sandoz/Momenta Question:
Sandoz/Momenta will detail the calculation in the test method and requests concurrence with approach.

**Sandoz/Momenta: Please see slide #2 for detailed explanation of [Redacted] (b) (4)
Calculation. The [Redacted] (b) (4)
[Redacted] The details of the method and the calculations
will be provided in the amendment.**

Teleconference Meeting Minutes



FDA: Your explanation appears to be plausible and we will take a look at the method details when you submit the amendment.

2. [Redacted] (b) (4)

Sandoz/Momenta Question:
Sandoz/Momenta will discuss the proposed revised specification and requests concurrence with proposal.

Sandoz/Momenta: We had responded to the deficiency regarding [Redacted] (b) (4) in our amendment in 2009. Based on the in-house data we have revised the specifications for [Redacted] (b) (4). Please see slide #3 for our proposed revised specs for [Redacted] (b) (4).

Question A.2: [Redacted] (b) (4) **Specification Proposal**

	(b) (4)
Current Specification	[Redacted]
Manufacturing Experience	[Redacted]
Proposed Specification	[Redacted]

	(b) (4)
Current Specification	[Redacted]
Manufacturing Experience	[Redacted]
Proposed Specification	[Redacted]



FDA: Your proposal to respond to deficiency #2 to tighten [Redacted] (b) (4) is acceptable.

Teleconference Meeting Minutes

3. [REDACTED] (b) (4)

Sandoz/Momenta Question:

Sandoz/Momenta has a release test and specification for [REDACTED] (b) (4)

[REDACTED]

(b) (4)

FDA: Your answer to deficiency #3 for [REDACTED] (b) (4) control is acceptable.

4. [REDACTED] (b) (4)

[REDACTED]

Sandoz/Momenta Question:

Sandoz/Momenta will discuss the proposed revised specification and requests concurrence with proposal.

Sandoz/Momenta: See slide #5 for our proposed response.

Teleconference Meeting Minutes

Question A.4: DP Unknown and Total Impurities
by (b) (4) **Specification Proposal**

Individual Unknown Impurity	
Current Specification	(b) (4)
Manufacturing Experience	
Proposed Specification	

Total Impurities	
Current Specification	(b) (4)
Manufacturing Experience	
Proposed Specification	

FDA: Your proposed specs for DP unknown and Total Impurities are acceptable.

5. [Redacted] (b) (4)

drug product.

Sandoz/Momenta Question:

Sandoz/Momenta will provide (b) (4) data from development drug product (along with RLD stability data) stability studies which showed no significant change. These data led Sandoz/Momenta to remove this test from the drug product stability program as a "for information only" test. Would submission of this data satisfy this request?

Sandoz/Momenta: We did not observe any increase in the (b) (4) when one RLD and four DP lots were monitored over 24 months. See slide #6 for our DP stability data.

We will check to see if we have data for stability testing (b) (4), if not we will provide a post approval stability commitment

FDA: We would like to see the data for the (b) (4)

Please provide data that shows there is (b) (4)

6. You have provided a list of quality control evaluations and testing of the incoming container/closure system (CCS) at your Novartis and (b) (4) facilities. You have also provided

Teleconference Meeting Minutes

one time study data for shipping and air transit simulation study as well as data for physical parameters. However, you have not provided data for the integrity and functional testing including volumetric accuracy, leak testing and needle penetration depth for given force for your container closure system, and the certificates of analysis (COAs) provided in your ANDA do not include these integrity and functional tests for your proposed CCS. Please provide these data and include these integrity and functional tests (with appropriate acceptance criteria) in the CCS COAs.

Sandoz/Momenta Question:

Per our September 3, 2014 teleconference, Sandoz/Momenta and FDA agreed to provide “a one-time test to ensure the quality of the syringe” which was provided in the CRL response dated October 1, 2014. Sandoz/Momenta will review the incoming component testing data provided in the ANDA and requests additional clarification regarding any additional information required.

Sandoz/Momenta: We had responded in the October 1 CR response. We are not sure why you are asking the same question again. See slide #8 for your question regarding CCS. We also have conducted shipping study and visual study.

Question A.6: Container/Closure

Request	Incoming Container Closure System Controls	Manufacturing Controls	Drug Product Controls
Volumetric Accuracy	(b) (4)		
Leak Testing			
Needle Penetration Depth			
Functional Testing			

8 Confidential and Proprietary MOMENTA

FDA: You did not provide data for leak testing, volumetric accuracy and needle penetration depth. The data provided for the integrity testing is not sufficient to know the leaks in the syringes. There are many tests commonly carried out to determine leaks in the pre-filled syringes such as dye ingress test which are mentioned in the FDA guidance for Industry for glass syringes. Such data could not be located in your submission.

Sandoz/Momenta: We performed microbial immersion test. Will this test along with integrity testing be sufficient for leak testing? We have in-house quality controls for the incoming lots of CCS which involves thorough functional testing of the syringes. No specific tests are performed to evaluate needle penetration depth but the needles are standardized and needle penetration differs from patient to patient. For evaluating volumetric integrity

Teleconference Meeting Minutes

fill volume and fill weight controls are included during manufacturing process. Therefore no separate volumetric integrity tests are carried out.

FDA: Microbial immersion test data is sufficient to demonstrate leak proof nature of the syringes. Integrity testing provided is acceptable.

B. Information Requested

Please provide details of analytical method for determining [REDACTED] (b) (4)

[REDACTED] and the validation report for the same.

FDA: No concern



3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
None	FDA	N/A
Respond to the ECD dated November 13, 2014	Sponsor	by COB November 19, 2014

5.0 ATTACHMENTS AND HANDOUTS

-  2014-09-03 - Sandoz Moment...
-  2014-09-08 - FDA Meeting Minut...
-  Sandoz Momenta Slides for FDA...

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/s/

SIMON S ENG
11/18/2014

KSHITIJ A PATKAR
11/18/2014

JING LI
11/18/2014

SAU L LEE
11/18/2014

ANDRE S RAW
11/19/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 090218

**TELECONFERENCE
MEETING MINUTES**

Sandoz, Inc.
Attention: Jean Domenico
Associate Director, Regulatory Affairs
2555 West Midway Blvd
Broomfield, CO 80038-0446

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL, dispensed in 1 mL prefilled syringes.

We also refer to the teleconference between representatives of your firm and the FDA on August 27, 2014. The purpose of the requested teleconference meeting was to discuss deficiencies noted in the Complete Response Letter dated August 19, 2014.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Simon Eng, Regulatory Project Manager at (240) 402-8932.

Sincerely,

{See appended electronic signature page}

Simon Eng, PharmD
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Post Complete Response Teleconference

Meeting Category: End of Review

Meeting Date and Time: August 27, 2014 at 2:30 p.m. EST

Application Number: 090218

Product Name: Glatiramer Acetate Injection, 20 mg/mL, dispensed in 1 mL prefilled syringes

Sponsor/Applicant Name: Sandoz, Inc.

Meeting Recorder: Simon Eng

FDA ATTENDEES

Sau (Larry) Lee, PhD, Act. Associate Director for Science, OPS

Jing Li, PhD, ANDA Reviewer, OPS

Kshitij (Kris) Patkar, PhD, ANDA Reviewer, OPS

Andre Raw, PhD, Division Director, ANDA Review Division 1, OPS

SPONSOR ATTENDEES

Sandoz Inc. attendees:

Anthony Maffia, Vice President, Regulatory Affairs

Linda O'Dea, Executive Director, Regulatory Affairs

Jean Domenico, Associate Director, Regulatory Affairs

Momenta attendees:

Kristina Storey, Associate Director, Regulatory Affairs

Christine Bell, Senior Director, Analytical Development

James Anderson, Vice President, Analytical Development

Jim Roach M.D., FACP, FCCP – Senior Vice President, Development and Chief Medical Officer

1.0 BACKGROUND

The meeting request was to clarify three of the deficiency comments in the CR letter dated August 19, 2014 for Glatiramer Acetate Injection, 20 mg/mL, dispensed in 1 mL prefilled syringes.



90218-27-14
TCON Question...

2.0 DISCUSSION

Below is a summary of the points discussed during the call, and is not intended to be a verbatim record of the discussion.

2.1. Category/Discipline A

Question 1:

Does the current inclusion of Mz as a measure of very high molecular weight, with the corresponding proposed acceptance criteria for Mz satisfy this request?

FDA Response to Question 1:

Your method of determining high molecular weight impurity using Mz parameter is not very clear. It doesn't show any retention time nor peak for such species in the chromatograms. Also, the method validation doesn't include high molecular weight species in the standards. Your method validation report should include qualitative and quantitative analysis of high molecular weight species.

Firm: We will have data from the forced degradation studies to show that our method can detect very low levels of high molecular weight species and we will point out in our CR response that our method of validation is sensitive to detect such species in samples. Molar mass determination by SEC-MALS-RI is a continuum method and Mz parameter is used to detect the presence of high molecular weight species. We will include the data for high molecular weight species in the CR response. We will show in our CR response that the method TP-300 can detect high molecular weight species using molar mass distribution parameters.

Question 2:

In addition to SEC-MALS, does the application of Turbidity/Clarity of Solution TP-105 and Particulate matter USP<788> tests to the drug product for release and stability satisfy the request for the additional test for aggregates?

Teleconference Meeting Minutes

The presence of larger particles which might be formed by excessive aggregation, would be detected in the drug product with the tests for turbidity (also known as clarity of solution) as well as the test for particulate matter (by USP<788>)..

FDA: You need to show us that you are able to detect the aggregates by the proposed methods and able to reject the batches based on the results. You need to show that turbidity method can detect particles with a range of sizes. The method validation report should include a threshold for the particle size detected. The data should be quantitative.

Question 3:

Does the testing conducted by both the syringe supplier and the drug product manufacturer satisfy this request for quality control testing of the container/closure system?

FDA: We have concern with the syringes supplied by the (b) (4) which had issues regarding (b) (4). Do you have in-house data to show that these syringes can withstand the pressure built up during the injection of the drug product? You may conduct a one-time testing to ensure the quality of the syringe.

Firm: We can provide data for the pressure test that show that the syringes proposed are suitable for the drug product.

Other questions:

Firm: We can respond to all the deficiency comments in a CR amendment response in three to six weeks. Some of the data you are requesting (Def#2 in the CR) will take more time to collect. As we have established sameness based on other data can we submit the data for (b) (4) analysis as a part of ongoing studies at a later time?

FDA: I am sorry. We need all your responses in one CR amendment.

Firm: Once we submit the CR amendment, will it be reviewed immediately and can you give us an estimated time which will take to complete the CR amendment review?

FDA: We understand the urgency to review the CR amendment. We will do our best to review it as soon as possible based on our limited resources. We cannot give you the time it takes to review the CR amendment.

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/s/

SIMON S ENG
09/08/2014

KSHITIJ A PATKAR
09/08/2014

JING LI
09/08/2014

SAU L LEE
09/08/2014

ANDRE S RAW
09/08/2014



ANDA 090218

MEETING REQUEST GRANTED

Sandoz, Inc.
Attention: Jean Domenico
Associate Director, Regulatory Affairs
2555 West Midway Blvd
Broomfield, CO 80038-0446

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL, dispensed in 1 mL prefilled syringes.

We also refer to your August 22, 2014, correspondence requesting a Post Complete Response Teleconference Meeting to discuss deficiencies noted in the Complete Response Letter dated August 19, 2014.

The teleconference is scheduled as follows:

Date: August 27, 2014

Time: 2:30 PM

Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

CDER Participants: Drs. Sau (Larry) Lee, Robert Lionberger, Jing Li, Kshitij (Kris) Patkar, Andre Raw and Simon Eng

Discussions will be summarized at the conclusion of the teleconference and reflected in FDA's meeting minutes.

If you have any questions, call Simon Eng, Regulatory Project Manager at (240) 402-8932.

Sincerely,

{See appended electronic signature page}

Simon Eng, PharmD
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

SIMON S ENG
08/27/2014



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Internal Meeting
Meeting Category: On-going Review
Meeting Date and Time: July 17, 2014

Application Number: 90218
Product Name: Glatiramer Acetate Injection
Sponsor/Applicant Name: Sandoz, Inc.

Meeting Recorder: Simon Eng, PharmD, Regulatory Project Manager

FDA ATTENDEES

Francis Godwin, Branch Chief, OC/OMPQ
Ruth Moore, Ph.D., Investigator, OC/OMPQ
Tracie Sharp, Compliance Officer, OC/OMPQ
Sau (Larry) Lee, PhD, Act. Associate Director for Science, OPS
Jing Li, PhD, ANDA Reviewer, OPS
Kshitij (Kris) Patkar, PhD, ANDA Reviewer, OPS

BACKGROUND

(b) (4), a contract testing laboratory was cited in the Form 483 during the (b) (4) inspection for the lack of (b) (4) studies; lack of the appropriate laboratory methods, method validation studies, laboratory equipment controls, and/or laboratory procedures for the specific application. Specifically, Method (b) (4) were used for release and stability testing of the drug product. However, the lab had not submitted an updated validation report including the (b) (4) (b) (4) studies or justification for the studies.

OC would like to know:

1. Is the Method acceptable as per CMC Review?

OPS: Method (b) (4) are two of the methods used for release and stability testing. However, these are not the only methods that determine the stability of the drug product. There are other analytical tests that are more sensitive in determining the stability of the drug product.

2. Were the methods validated? Did CMC review these?

OPS: We did, but they were not consistent. We will issue Sandoz a CR and ask them which method ((b) (4)) will be used consistently. Again, one of these methods would serve the purpose but it should not be considered as the only method. For example, Molecular Distribution is more sensitive than one of these methods.

3. Were these method validations verified on site?

OPS: No, we will issue Sandoz the CR letter and request them to conduct validation on site after getting clarification about which method will be used in the future for the release and stability testing. We will need OC to provide the proper language we should use in the CR letter.

Action Item/Description	Owner	Due Date
Provide OPS Chemist a statement in the CR letter to indicate which is a valid method and the method chosen has to be validated at (b) (4)	Office of Compliance	By COB 7-25-14

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/s/

SIMON S ENG
07/23/2014

SAU L LEE
07/30/2014



ANDA 090218

**TELECONFERENCE
MEETING MINUTES**

Sandoz Inc.
Attention: Jean Domenico
Associate Director, Regulatory Affairs
2555 West Midway Blvd.
Broomfield, CO 80038

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/1 mL, dispensed in 1 mL prefilled syringes.

We also refer to the teleconference between representatives of your firm and the U.S. Food and Drug Administration (FDA) on June 18, 2014. The purpose of the requested teleconference meeting was to discuss FDA's request for additional drug samples to be analyzed in FDA's St. Louis Lab.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Simon Eng, Regulatory Project Manager at (240) 402-8932.

Sincerely,

{See appended electronic signature page}

Simon Eng, PharmD
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Post Complete Response Teleconference
Meeting Category: End of Review
Meeting Date and Time: June 18, 2014

Application Number: 090218
Product Name: Glatiramer Acetate Injection, 20 mg/mL
Sponsor/Applicant Name: Sandoz Inc.

Meeting Recorder: Simon Eng, PharmD, Regulatory Project Manager

FDA ATTENDEES

Sau (Larry) Lee, PhD, Act. Associate Director for Science, OPS
Jing Li, PhD, Reviewer, OGD CMC
Kshitij (Kris) Patkar, PhD, Reviewer, OGD CMC
Xiaohui Jiang, PhD, Science Reviewer, OGD Science Staff

SPONSOR ATTENDEES

Momenta

Jennifer Smith, PhD, VP, Quality
Jim Roach, MD, SVP, Development and Chief Medical Officer
Ganesh Kaundinya, PhD, Chief Scientific Officer
John Bishop, PhD, SVP, Pharmaceutical Sciences

Sandoz

Jean Domenico, Regulatory Affairs
Nick Tantillo, Regulatory Affairs

1.0 BACKGROUND

Sandoz and Momenta asked for a short telephone meeting with OGD in order to better understand the reasons for requesting additional drug samples and the proposed tests which will be conducted in the FDA St. Louis Lab.

The current request for drug samples is as follows:

- 3 lots of Glatiramer Acetate Injection (1 syringe each),
- 3 lots of Copaxone (1 syringe each) and
- 1 lot of negative control Lot FA0907-051-001 (~40 mg).

Previously, OGD had requested and received 100 syringes of Glatiramer Acetate Injection, 50 syringes of Copaxone and 100 mg of negative control (Lot FA0907-051-001) in December 2013.

Sandoz and Momenta called OGD on June 13, 2014, inquiring as to the reason FDA requested the applicants to submit additional drug samples. Simon Eng from OGD asked Sandoz and Momenta to email their questions and concerns to OGD. OGD's responses to their questions were sent to Sandoz on June 16, 2014, via email. They were as follows:

1. Is our understanding of the sample request correct?

Yes

2. Is it acceptable to provide the negative control Lot FA0907-051-001 as a solid drug substance, which is the same state in which we previously provided it to the St. Louis lab?

Please provide the negative control formulated in the drug product formulation with mannitol. Formulating the negative controls into a drug product will help our analytical analysis of these samples. Note the sample needs not be sterile nor be filled in a syringe (a vial is acceptable). The dosage of the negative controls should be identical to the drug product. This is critical.

3. Please provide additional details regarding the purpose of this sample request including which tests the material will be used in. Will the St Louis lab be using the same testing protocol for these new samples as it did for the samples provided in December of last year?

The FDA will conduct an analytical analysis of these samples using the in-house methods. However, this will not interfere with our review timelines of your application.

4. Please provide the anticipated timing in which this testing will be completed.

See answer #3.

Sandoz and Momenta contacted the Office of Chief Counsel and OGD on June 16, 2014, and June 17, 2014, respectively, requesting additional assurance that the request for additional drug samples and testing will not delay the review and approval of ANDA 090218.

2.0 DISCUSSION

Below is a summary of the points discussed during the call, and is not intended to be a verbatim record of the discussion.

Firm: We have formulated the negative control samples. We have delivered the negative control and other requested samples to you today already. What is the reason for such a request, and which methods are you using to test them?

FDA: The reason for the testing these drug samples is to have an independent analysis by our FDA testing laboratory in St. Louis. Such an independent analysis by the FDA is typically done for products containing complex drug substances.

Due to complexity of the drug substance, we requested for more lots of the drug sample in part because we want to have a better understanding of the variability of the RLD samples and confirm our previous results based on our in-house method. We understand complexity of the drug substance and we know that it cannot be characterized by a single method, but rather by a combination of multiple methods (include characterization of structural signatures that reflect the process kinetics).

Firm: We wanted to make sure these tests are not intent to address additional concerns raised during the review process.

FDA: These tests are not addressing any specific concern raised during review.

Firm: Are these tests chemical tests or biologic tests?

FDA: We cannot comment on this question.

Firm: Can you tell me about the compliance issues with (b) (4) testing lab?

FDA: Our reviewers will discuss the issues of (b) (4) study data which was cited by the inspector in the Form 483 during the recent inspection of (b) (4) Testing Lab. We will provide comments to the ORA District Office/Office of Compliance (OC) so that OC can give us an overall recommendation for the ANDA. We are working very hard to resolve this critical issue. The EIR is under review and the CMC is under review. If we have any questions during the review, we will communicate with you as soon as we can through our current review practice. We understand the urgency in reviewing the application.

3.0 ACTION ITEM

Action Item/Description	Owner	Due Date
Compliance issue with (b) (4) Testing Lab	FDA	Will provide comment to ORA to resolve the Form 483 issues by 25-JUN-14

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/s/

SIMON S ENG
06/20/2014



ANDA 090218

MEETING REQUEST GRANTED

Sandoz Inc.
Attention: Jean Domenico
Associate Director, Regulatory Affairs
2555 West Midway Blvd.
Broomfield, CO 80038

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL, dispensed in 1 mL prefilled syringes.

We also refer to your June 17, 2014 email request, and correspondence submitted on June 18, 2014 requesting a Teleconference Meeting to discuss the reason for our request for additional drug samples.

The teleconference is scheduled as follows:

Date: June 18, 2014
Time: 2:30 P.M. EST

Phone Arrangements:

DIAL IN INFORMATION:

ACCESS (Dial In) NUMBERS:

1-866-755-6294 (Toll-Free North America)

Participant Passcode: [REDACTED] (b) (4)

CDER Participants: FDA ATTENDEES

Sau (Larry) Lee, PhD, Act. Associate Director for Science & Research
Jing Li, PhD, Reviewer
Kshitij (Kris) Patkar, PhD, Reviewer
Xiaohui Jiang, PhD, Science Reviewer

Discussions will be summarized at the conclusion of the teleconference and reflected in FDA's meeting minutes.

If you have any questions, call Simon Eng, Regulatory Project Manager at (240) 402-8932.

Sincerely,

{See appended electronic signature page}

Simon Eng, PharmD
Regulatory Project Manager
Division of Project Management
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

SIMON S ENG
06/20/2014

Eng, Simon

From: Eng, Simon
Sent: Wednesday, June 18, 2014 10:50 AM
To: 'Tantillo, Nicholas'; Domenico, Jean
Cc: Hansen, Lara
Subject: RE: Sandoz Glatiramir Injection, ANDA 090218

You are welcome Nick and Jean.

From: Tantillo, Nicholas [mailto:nicholas.tantillo@sandoz.com]
Sent: Wednesday, June 18, 2014 10:49 AM
To: Domenico, Jean; Eng, Simon
Cc: Hansen, Lara
Subject: RE: Sandoz Glatiramir Injection, ANDA 090218

Hi Simon,
Thanks for pulling the team together for a meeting on such short notice. We'll do our part to keep it short and sweet.
Nick

Nicholas Tantillo
Vice President, Reg. Affairs
Sandoz Inc., East Hanover Site
One Health Plaza
Bldg. 435
East Hanover, NJ 07936-1080
USA

Phone +1 862 7780955
Fax +1 973 7813710
Mobile +1 (b) (6)
nicholas.tantillo@sandoz.com
www.novartis.com

From: Domenico, Jean
Sent: Wednesday, June 18, 2014 10:38 AM
To: Simon.Eng@fda.hhs.gov
Cc: Tantillo, Nicholas; Hansen, Lara
Subject: RE: Sandoz Glatiramir Injection, ANDA 090218

Thank you Simon !

From: Eng, Simon [mailto:Simon.Eng@fda.hhs.gov]
Sent: Wednesday, June 18, 2014 8:28 AM
To: Domenico, Jean
Cc: Tantillo, Nicholas; Hansen, Lara
Subject: RE: Sandoz Glatiramir Injection, ANDA 090218

Thank you Jean and Nick.
Thanks for sending the samples to St. Louis.
On our side we have Jing Li, Larry Lee, Xiaohui Jiang, Kris Patkar and myself.

We will call you at 230pm with the # you have provided.

Thanks,

Simon

From: Domenico, Jean [<mailto:jean.domenico@sandoz.com>]

Sent: Wednesday, June 18, 2014 10:02 AM

To: Eng, Simon

Cc: Tantillo, Nicholas; Hansen, Lara

Subject: RE: Sandoz Glatiramir Injection, ANDA 090218

Good Morning Simon,

I believe that Nick confirmed we can meet today at 2:30 p.m. Eastern Time. Please use the dial in information we have provided below. Also, if you can provide me with the FDA names that will be on the call, that would be great. In addition, I am back in the office for a while, so if you have further questions regarding this meeting, please let me know. I am pleased that Nick has been able to help out in setting up this meeting in my absence. But, I am back in the office and am here if anything should come up in the meantime.

Also, I wanted to let you know that we sent the samples to the St. Louis lab yesterday via overnight mail, for receipt today. Attached is a copy of the letter that was enclosed. We are also filing an amendment today (Seq 0066) to our application letting you know that the samples were sent. A copy of cover letter for Sequence 0066 is also provided for your reference.

We look forward to our discussion today. Thank you again for coordinating this meeting with your team.

Sincerely,

Jean

Jean Domenico

Associate Director, Regulatory Affairs

Sandoz Inc.

2555 West Midway Boulevard

Broomfield, CO 80020

USA

Direct Phone +1 303 4384242

Cell Phone +1 (b) (6)

Fax +1 303 4384600

jean.domenico@sandoz.com

www.novartis.com

From: Eng, Simon [<mailto:Simon.Eng@fda.hhs.gov>]

Sent: Wednesday, June 18, 2014 5:23 AM

To: Tantillo, Nicholas; Domenico, Jean

Subject: RE: Sandoz Glatiramir Injection, ANDA 090218

Hi Nick and Jean,

I think we can hold the TCON at 230pm EST, can you see if your team can make it? Only two in my team have accepted my invitation. I am still waiting for 3.

Let me know.

From: Tantillo, Nicholas [<mailto:nicholas.tantillo@sandoz.com>]

Sent: Tuesday, June 17, 2014 2:14 PM

To: Eng, Simon

Subject: Sandoz Glatiramir Injection, ANDA 090218

Hi Simon,

Further to our conversation earlier today, I want you to know that we are actively preparing the samples submission and will send it to the following address later today or tomorrow:

Attention Sample Custodian: Brian Noakes
For Drs. David Keire and Michael Boyne
Food and Drug Administration
Division of Pharmaceutical Analysis
645 South Newstead
St. Louis, Missouri 63110 USA

Simon, Sandoz and Momenta are also asking for a short telephone meeting as soon as possible with the relevant FDA scientists in order to better understand the proposed testing the St Louis Lab will be undertaking and to offer any advice or assistance we can based on Momenta's extensive experience testing the product.

Here is a list of attendees for the call:

Momenta

Jennifer Smith, PhD, VP, Quality
Jim Roach, MD, SVP, Development and Chief Medical Officer
Ganesh Kaundinya, PhD, Chief Scientific Officer
John Bishop, PhD, SVP, Pharmaceutical Sciences

Sandoz

Jean Domenico, Regulatory Affairs
Nick Tantillo, Regulatory Affairs

We will make ourselves available for this call at your earliest convenience.

DIAL IN INFORMATION:

ACCESS (Dial In) NUMBERS:

1-866-755-6294 (Toll-Free North America)

1-973-947-7807 (International)

Participant Passcode: (b) (4)

In closing, I want to thank you for the ongoing care and attention you give to this important application. I look forward to hearing from you shortly.

Regards,
Nick

Nicholas Tantillo

Vice President, Reg. Affairs
Sandoz Inc., East Hanover Site
One Health Plaza
Bldg. 435
East Hanover, NJ 07936-1080
USA

Phone +1 862 7780955

Fax +1 973 7813710

Mobile +1 (b) (6)

nicholas.tantillo@sandoz.com

www.novartis.com

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/s/

SIMON S ENG
06/19/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2014-0927	
TO (Division/Office) Office of Clinical Pharmacology/OPS Thru: Tom Colatsky And cc: Mike Pacanowski			FROM: Simon Eng OGD RPM	
DATE: 5/23/2014	IND NO.	ANDA NO. 90218 Sandoz (b) (4) NDA: TEVA 20622	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 5/12/2014,
NAME OF DRUG Glatiramer Acetate Injection		PRIORITY CONSIDERATION 15 days	CLASSIFICATION OF DRUG Neurology Product for Multiple Sclerosis	DESIRED COMPLETION DATE 6/7/2014
NAME OF FIRM Sandoz/Momenta ANDA 90218 (b) (4) NDA TEVA 20622				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT X OTHER ('specify below) <input type="checkbox"/> MEETING PLANNED BY _____				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input checked="" type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> PROTOCOL-- BIOPHARMACEUTICS <input type="checkbox"/> IN--VIVO WAIVER REQUEST			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS(List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS Dear OCP, 1 - Evaluate the data quality, sample variability (including method and batch to batch variability) and analytics and statistics used by TEVA on their gene expression studies related to comparing RLD Copaxone to generics. TEVA has published on this and made their raw data available to include an analysis of their raw data publicly available in the GEO array data repository (GSE40566). 2 - Are comparative data from these sorts of studies valuable to the assessment of sameness for generic Copaxones? a) Are there any reliable differences between the RLD batches and generic samples in individual gene expression or pathways in the TEVA studies? b) Are any of the differences biologically plausible as relevant to product safety of efficacy (with OGD & OBP) c) If the answer to both (a) and (b) is yes, is there a feasible and robust experimental approach to test generic candidate products TEVA NDA 20622-I have requested NDA on 5-22-14 to provide the lot# which was used in the summary of gene expression experiments ANDA: Sandoz/Momenta 90218 data in SD#71 in DARRTS dated 5-12-14 (b) (4) Please provide an electronic copy of the review to the requestor by email and cc Steven Yang, HFD-617 (Steven.Yang@FDA.HHS.gov) when it is being checked into DARRTS. Thank you.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	

Simon Eng	
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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/s/

SIMON S ENG
05/23/2014



ANDA 090218

Sandoz Inc.
Attention: Jean Domenico
Associate Director, Regulatory Affairs
2555 West Midway Blvd.
Broomfield, CO 80038

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/1 mL, dispensed in 1 mL prefilled syringes.

Reference also is made to the General Advice letter we sent you on March 24, 2014, in which we informed you that presentation materials from a listening session between FDA and TEVA Pharmaceutical Industries, Ltd. (TEVA), which took place on February 25, 2014, had been submitted to Docket FDA-2013-P-1641 and were available at <http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1641-0004>.

In the General Advice letter, we expressly noted that we were not taking any position on the substantive issues raised in TEVA's presentation. However, if you have conducted any targeted gene expression studies similar to those described in the presentation, and also published (Bakshi, S, et al. *Expert Opin Ther Targets*, 17(4):351-362 (2013)), we request that you submit such data/studies to your ANDA. Data from other technologies, such RNA-seq, also would be of interest.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

ROBERT L WEST

05/07/2014

Deputy Director, Office of Genertic Drugs, for
Kathleen Uhl, M.D.

Eng, Simon

To: Eng, Simon
Subject: FW: Momenta Business 90218

From: Uhl, Kathleen (CDER)
Sent: Tuesday, May 06, 2014 7:57 AM
To: 'Craig Wheeler'
Cc: Eng, Simon
Subject: RE: Momenta Business

Craig,
You could submit any comments, data, analysis, etc. that Momenta has directly to your ANDA.
Cook

Kathleen Uhl, MD
Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research, FDA
10903 New Hampshire Ave.
WO Bldg 75, Rm 1692
Silver Spring, MD 20993
240-402-7920

From: Craig Wheeler [<mailto:cwheeler@momentapharma.com>]
Sent: Monday, May 05, 2014 4:05 PM
To: Uhl, Kathleen (CDER)
Subject: Momenta Business

Cook,

As you probably know, the FDA responded to Teva's latest CP last Friday. The FDA's legal team has informed our counsel that we should not respond to a closed CP docket, and that we should seek advice from the division on the best next steps. Can you spare a few minutes to talk in the next day or so.

Thanks,
Craig

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/s/

SIMON S ENG
05/06/2014

Eng, Simon

From: Uhl, Kathleen (CDER)
Sent: Thursday, May 01, 2014 10:22 AM
To: Eng, Simon
Subject: communication with Craig Wheeler of Momenta

Simon,

Can you enter this email into the record for the Momenta/Sandoz ANDA 090218 on Glatiramer.

I spoke with Craig Wheeler about the status of their application today. He indicated that they had communication from the RPM on 4/24 that approval on the patent expiry date in May was not going to happen. I told him that there were still internal discussions at FDA about next steps and that they should anticipate more formal communication from the Agency in the next few weeks.

He mentioned that Mylan had submitted a document to the docket on the Teva CPs, rebutting the gene expression analysis done by Teva. He informed me that Momenta/Sandoz had not sent anything and I indicated that their analysis of the science would be welcome by FDA as well.

Thanks,
Cook

Kathleen Uhl, MD
Acting Director
Office of Generic Drugs
Center for Drug Evaluation & Research, FDA
10903 New Hampshire Ave.
WO Bldg 75, Rm 1692
Silver Spring, MD 20993
240-402-7920

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/s/

SIMON S ENG
05/01/2014



ANDA 090218

Sandoz Inc.
Attention: Jean Domenico
Associate Director, Regulatory Affairs
2555 West Midway Blvd.
Broomfield, CO 80038

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received on December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/1 mL, dispensed in 1 mL prefilled syringes.

In the interests of transparency, we write to notify you, as a sponsor of an ANDA for Copaxone (Glatiramer Acetate Injection) 20 mg/mL, that presentation materials from a listing session between FDA and Teva Pharmaceutical Industries, Ltd., which took place on February 25, 2014, have been submitted to Docket FDA-2013-P-1641, available at <http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1641-0004>.

In providing you this notice, we are not taking any position on the substantive issues raised in the slides. If you have any comments on these materials, please submit them to the docket, and/or to your ANDA.

Sincerely yours,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

SIMON S ENG

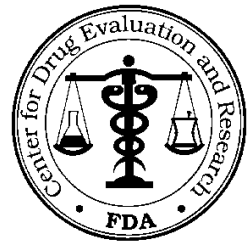
03/24/2014

RPM on behalf of Kathleen Uhl, M.D., Acting Director, Office of Generic Drugs

EASILY CORRECTABLE DEFICIENCY FAX

ANDA 090218

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Sandoz Inc.

TEL: 303-438-4242

ATTN: Jean Domenico

FAX: 303-438-4600

FROM: Simon Eng

FDA CONTACT PHONE: (240) 276-8529

Dear Madam:

This communication is in reference to your abbreviated new drug application (ANDA) dated December 26, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**EASILY CORRECTABLE DEFICIENCY
LABELING**

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Regulatory Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

If you have questions regarding these deficiencies please contact the Regulatory Project Manager, Simon Eng at (240) 276-8529.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

We have completed our review, and have the following comments:

LABELING:

Labeling Deficiencies determined on March 12, 2014, based on your submission dated February 12, 2014:

1. CONTAINER

Please submit syringe samples and ensure that the labels could be easily read.

2. BLISTER

Add directly above the “Keep refrigerated ...” statement,

“FOR SUBCUTANEOUS INJECTION ONLY

ONCE DAILY”

If space is at a premium, you may delete the needle information, “Supplied as 1 mL single dose...”

Refer to the Reference Listed Drug’s labeling for guidance.

3. CARTON

Add “ONCE DAILY” to appear directly above “Glatopa”. “ONCE DAILY” should be the same type size as the established name “glatiramer acetate injection”. Refer to the Reference Listed Drug’s labeling for guidance.

4. PRESCRIBING INFORMATION/PHYSICIAN INSERT

- a. HIGHLIGHTS, DOSAGE AND ADMINISTRATION, first bullet, revise to state “For subcutaneous injection only, Glatopa 20 mg per mL dose is not interchangeable with glatiramer acetate 40 mg per mL dose.
- b. 2.1 Recommended Dose, add “Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable”.
- c. 17 PATIENT COUNSELING INFORMATION, Instructions for Use, add the following as the second sentence in this subsection: “Glatopa 20 mg per mL and glatiramer acetate injection 40 mg per mL are not interchangeable.”

5. PATIENT INFORMATION and INSTRUCTION FOR USE

What is your plan to ensure that each patient receives these labeling pieces upon dispensing?

Submit your revised labeling electronically in final print format.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained.

Prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the Electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17.

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

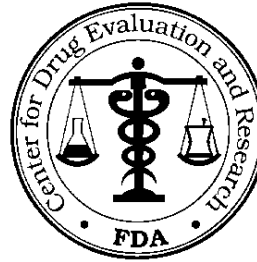
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/s/

JULIE M CALL
03/19/2014

FDA FAX

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: SANDOZ INC

TEL: 303-438-4242

ATTN: Jean Domenico

FAX: 303-438-4600

This facsimile is in reference to your abbreviated new drug application(s), submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Pages (including cover): 4

SPECIAL INSTRUCTIONS:

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

DATE: 2/10/2014

TO: SANDOZ INC

ATTN: Jean Domenico

E-Mail: jean.domenico@sandoz.com

FAX: 303-438-4600

RE: Update summary of filed and pending original ANDA(s)

Dear Sir or Madam:

The Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is providing you with this one-time communication on the status of your filed and pending original abbreviated new drug application(s) (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act. OGD is providing these updates as an interim measure to help applicants assess the status of their current submissions as we transition towards predictable goal times pursuant to the Generic Drug User Fee Amendments of 2012 (GDUFA).

Your status update is limited to available review information as of January 29, 2014. Any additional information regarding your ANDA collected after this date is neither considered nor provided. Furthermore, your ANDA status is subsequently subject to revision pending additional information or concerns raised by any of the discipline reviews (bioequivalence, clinical, chemistry, microbiology, labeling, facility), other unforeseen legal, scientific or regulatory issues, or inspectional results, which can also impact the status or ability to issue a complete response. Any applicable fees can also affect the status of your ANDA.

OGD is providing your ANDA status update in the attached chart with a list of applicable acronyms. The chart only contains current information regarding discipline review and does not forecast if and when OGD will issue a complete response, tentative approval, or final approval letter.

Please do not respond to this communication by asking FDA or your Regulatory Project Manager for additional or more detailed information. This is a one-time communication intended to assist you to ascertain the current status of submissions. It is not feasible for us to respond to a high volume of follow up inquiries.

Sincerely yours,

CAPT Aaron W. Sigler, USPHS
Chief, Review Support Branch

ANDA	DRUG NAME	CHEM	BIO	MICRO	LABEL	CLINICAL	FACILITY
	(b) (4)	UR	AQ	NA	IQ	NA	AC
	(b) (4)	NR	NR	NA	IQ	NA	AC
	(b) (4)	NR	NR	NA	UR	NA	AC
78467	ESCITALOPRAM OXALATE	AQ	AQ	NA	AQ	NA	PN
	(b) (4)	AQ	AQ	NA	AQ	NA	PN
90218	GLATIRAMER ACETATE	UR	AQ	IQ	UR	NA	PN
90296	PANTOPRAZOLE SODIUM	AQ	AQ	AQ	AQ	NA	PN
	(b) (4)	UR	IQ	IQ	IQ	UR	PN
91232	NORGESTIMATE/ETHINYL ESTRADIOL	AQ	AQ	NA	AQ	NA	PN
91635	TROSPIUM CHLORIDE	AQ	UR	NA	AQ	NA	PN

CHART ACRONYMS

Column Headings

ANDA	- The application number for your Abbreviated New Drug Application
DRUG NAME	- The official filed name of the drug associated with the ANDA number
CHEM	- Product Quality Chemistry Review
BIO	- Bioequivalence Review, typically including OSI, if applicable
MICRO	- Microbiology Review
LABEL	- Labeling Review
CLINICAL	- Clinical Review
FACILITY	- Overall Facility inspections summary. All facilities must be acceptable at the time of 29 JAN 14 in order to warrant an adequate notation. If one of more facility is not acceptable then the FACILITY column will be marked as such. OSI information is not considered.

Discipline Notations

- IQ - Inadequate. This particular discipline is currently found to be inadequate.
- AQ - Adequate. This particular discipline was found to be adequate when the information was gathered for this communication.
- UR - Under Review. This particular discipline is currently assigned OR under review with the discipline team.
- NR - Not Reviewed. This particular discipline is either currently not under review or assigned.
- NA - Not applicable. This particular discipline is not required for the approval of this ANDA.

Facility Notations

- PN - Pending, i.e., one or more facilities have been inspected and are pending an outcome.
- AC - All facilities are acceptable at the time of this publication.

*Please note that you may receive your updates in multiple communications over time, based on the number of ANDAs pending in OGD.

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/s/

SIMON S ENG on behalf of AARON W SIGLER
02/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION Consult No: 2014-0894	
TO (Division/Office) OBP: Marilyn Welschenbach			FROM: Jing Li	
DATE: 1/31/2014	IND NO.	ANDA NO. 000218 (b) (4)	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 7/12/2011,9/26/2012; 7/26/2011, 3/22/2012; 12/1/2011
NAME OF DRUG Glatiramer Acetate		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Multiple Sclerosis	DESIRED COMPLETION DATE 4/1/2014
NAME OF FIRM Sandoz/ Momenta (b) (4)				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY _____		<input type="checkbox"/> PRE NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER ('specify below')
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> PROTOCOL-- BIOPHARMACEUTICS <input type="checkbox"/> IN--VIVO WAIVER REQUEST			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS(List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS OGD is requesting a consult to OBP regarding the biological and immunological assays for glatiramer acetate. (b) (4) in vitro and in vivo bioassay data (b) (4) and provide comment on whether currently available data are sufficient to demonstrate drug substance sameness from the biology and immunology perspective. The relevant data and literature will be sent to OBP by E-mail. Please provide an electronic copy of the review to the requestor by email and cc Steven Yang, HFD-617 (Steven.Yang@FDA.HHS.gov) when it is being checked into DARRTS. Thank you.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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/s/

JING LI
01/31/2014

STEVEN W YANG
02/03/2014

Minutes of a Meeting

Meeting Date: January 28, 2014

Company: Sandoz Inc.

Product: ANDA 90218
Glatiramer Acetate Injection

Type of Meeting: Internal

Attendees:

Office of Generic Drugs (OGD)

Kathleen (Cook) Uhl, M.D., Acting Director of OGD
Bob West, M.S., Deputy Director of OGD
Andre Raw, Ph.D., Director of DC1/OGD
Sau (Larry) Lee, Ph.D., Acting Associate Director for Research Policy and Implementation/OPS
Jing Li, Ph.D., Chemistry Reviewer, DC1/OGD
Kshitij (Kris) Patkar, Ph.D., Chemistry Reviewer, DC1/OGD
Rob Lionberger, Ph.D., Acting Director for Office of Research and Standards
Xiaohui Jiang, Ph.D., Science Staff
Kim McCullough, RPh, MBA, Project Manager
Trellis Adams, RN, Project Manager
Simon Eng (Meeting Recorder), Pharm.D, Project Manager

Office of Biotechnology Products (OBP)

Daniela Verthelyi, M.D., Ph.D., Chief, Laboratory of Immunology, DTP/OBP
Steven Kozlowski, M.D., Director of OBP
Amy Rosenberg, M.D., Director of DTP/OBP
Frederick Mills, Ph.D. Staff Scientist, DTP/OBP

Background:

Glatiramer Acetate Injection (RLD: Copaxone from TEVA) is indicated for the treatment of Multiple Sclerosis. The patent will expire on 5-24-2014. (b) (4)

The drug substance is a complex mixture of polypeptides and the mechanism(s) of action involves multiple pathways. OGD would brief the OBP about their understanding of GA from the CMC perspective, and seek opinions of OBP regarding the need for the biological and immunological analysis.

Main Discussion Points:

OGD gave an overview of the GA synthesis process and the drug substance sameness determination. OGD currently believes that the risk of this drug product is low from a sameness perspective due to the well understood reaction kinetics, robust synthesis process, and well-characterized key structural fingerprints or local sequences. The main discussion points in the OGD presentation included the following.

- The drug substance is best defined by its structural fingerprints, which reflect the reaction kinetics of the synthesis process and are preserved from batch to batch. Equivalence of the structural fingerprints demonstrates drug substance sameness, which in turn will indicate equivalent reaction kinetics used to manufacture the proposed generic and innovator glatiramer acetate drug substances.
- The synthesis process is relatively insensitive to process parameters. The synthesis of the drug substance is a relatively simple chemical process, because the underlying chemistry and kinetics is well understood and documented in literature. In addition the surface response curve of the polymerization structural fingerprints is relatively flat. Therefore, the development data show that as long as the starting materials (b) (5), and the synthesis is conducted in the reasonable operating ranges, the likelihood of producing glatiramer acetate equivalent to that found in the RLD by a generic manufacturer is very high.
- The primary characterization of the structural fingerprints is believed to be sufficient for the purpose of sameness demonstration. A set of analytics with high sensitivity and specificity were developed and used to characterize the structural fingerprints. All the comparative study results demonstrated drug substance sameness between the proposed generic and the RLD product. Almost all the test results are expected or explainable based on our fundamental understanding of the underlying chemistry and kinetics. Furthermore, additional secondary characterization (e.g., peptide mapping of microsequences) were conducted to further confirm drug substance sameness of the proposed generic and the RLD product.
- The characterization of the secondary structure and aggregation property was also conducted. The higher order structure is thermally and chemically reversible and thus the equivalence can be inferred primarily from equivalence in the primary structure that is defined by a fundamental set of structural fingerprints. The aggregation phenomenon is also well characterized and understood (results from tyrosine cross-linking). Thus the risk of aggregation of the drug substance appears to be low under recommended storage conditions, and will be further evaluated in the context of drug product in the next review cycle.

OBP asked questions and expressed concerns regarding the mechanism(s) of action for glatiramer acetate and the existence of possible microsequences responsible for the mechanism(s) of action. At the time of meeting, OBP suggested a human clinical study as well as alternatives such as preclinical and in vitro studies to further support evaluation of the proposed generic glatiramer acetate. Due to the complexity associated with this drug, OBP agreed to evaluate the in vitro/in vivo bioassays contained in the ANDAs, which may be helpful in

determining what additional studies will be needed for evaluation of the proposed generic glatiramer acetate.

Action items:

1. OGD peptide team will draft a formal consult request to OBP to evaluate the biocharacterization data contained in the ANDA applications.
2. OGD will hold another meeting with OBP after they have completed the consult and discuss about the next step.
3. The 6th CP from Teva will be made available to OBP. Representatives from OBP and OGD will attend Teva face-to-face meeting and the ORP meetings regarding TEVA CP.

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/s/

SIMON S ENG
02/28/2014

ROBERT A LIONBERGER
02/28/2014

ANDRE S RAW
03/04/2014

SAU L LEE
03/04/2014

From: Eng, Simon [<mailto:Simon.Eng@fda.hhs.gov>]
Sent: Monday, December 09, 2013 9:18 AM
To: Hansen, Lara
Cc: Eng, Simon
Subject: RE: 90218 Glatiramer Inj Sandoz
Importance: High

Hi Lara,

We contacted our analytical chemist. He needs 20 syringes of 20 mg/mL strength, 1 mL volume for the drug product (generic and negative control) and 100 mg of drug substance and drug substance negative control for the analysis.

(Consider negative controls as almost like a different product. You need to manufacture the negative controls as drug products. We need 20 of these syringes. You also need to manufacture negative control drug substance, we will need 100 mg of that.)

Thanks,

Simon

From: Hansen, Lara [<mailto:lara.hansen@sandoz.com>]
Sent: Friday, December 06, 2013 3:24 PM
To: Eng, Simon
Subject: RE: 90218 Glatiramer Inj Sandoz

Hi Simon,

Thank you for your feedback, will you be able to clarify the needs for the drug substance and negative controls requested. Specifically, how much volume is the reviewer needing?

Thanks again,

Lara

From: Eng, Simon [<mailto:Simon.Eng@fda.hhs.gov>]

Sent: Friday, December 06, 2013 7:13 AM

To: Hansen, Lara

Subject: FW: 90218 Glatiramer Inj Sandoz

Hi Lara,

Please send 100 syringes of your generic and 50 syringes of RLD to OGD, attention Kathleen Uhl, MD.

Thanks,

Simon

Dear Simon,

I left you a voicemail yesterday regarding your response below, but am following up with an email outlining our inquiries, which are not pre-submission review questions, but more OGD process related items. Please feel free to call me to discuss.

1. In the CRL, it is noted on page 1 that FDA "has completed our review of this ANDA." However, on page 2, it is noted that "upon addressing these deficiencies, we will undertake the review of remaining sections of the drug substance module, including biocharacterization and the drug product in your ANDA." If the ANDA was not completely reviewed, please clarify the review process moving forward, as this approach is inconsistent with our understanding of the GDUFA review process. Should we anticipate an iterative review and what should our expectations be regarding turnaround of our responses and receipt of additional questions?
2. Sandoz/Momenta believes that the scope of the questions asked are aligned with a "Minor" designation as we do not need to manufacture new batches, conduct a BE study or revalidate our process. As the deficiencies are easily addressed and will be filed within the next 1-2 weeks, we believe CRL should be treated as "Minor." Does the Agency concur?

3. Sandoz/Momenta intends to file our response to the CRL no later than mid-December. How will these responses be prioritized within OGD? Will the review team be able to review our response upon submission and continue to review the remaining ANDA sections immediately, or will our response be placed in a review queue to be picked up at a later date?
4. Please clarify how much of each sample is required and the address for the agency laboratory where samples should be sent. Please specify Agency requirements for the negative control samples.

Thanks again for your assistance and I look forward to hearing from you regarding our inquiries.

Kind Regards,
Lara

Lara Hansen

Sandoz Inc.

Regulatory Affairs

Broomfield, CO USA

1-303-438-4353

lara.hansen@sandoz.com

www.sandoz.com

From: Eng, Simon [<mailto:Simon.Eng@fda.hhs.gov>]

Sent: Wednesday, December 04, 2013 1:23 PM

To: Hansen, Lara; Domenico, Jean

Subject: 90218 Glatiramer Inj

Hi Jean and Lara,

I spoke with the reviewer and the team leader about the CR letter. They felt strongly that the deficiencies outlined on the letter are very clear and you should be able to respond with the amendment. We cannot conduct a presubmission review in any way or form. Please submit your response as soon as possible and we go from there.

Thanks,

Simon

Simon Eng, Pharm.D.

CAPT, USPHS

PEPTIDE and Injectable Team PM

OGD/CDER/FDA

7500 Standish PL, Rockville, MD 20855 MPN-2, RM E-222 P: 240-276-8529/F: 240-276-8504

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/s/

SIMON S ENG
12/09/2013

MEMO TO FILE

To: ANDA 090218

Subject: Glatiramer Acetate Injection, 20 mg/mL

Dr. Uhl spoke with Craig Wheeler on June 13, 2013 and gave him an update that ANDA 090218 is currently under review, by several disciplines, and that it would be several months until they hear back from us.

FROM THE DESK OF...

**SAUNDRA T. MIDDLETON
CDER\FDA\OGD\IO
7519 STANDISH PLACE
ROCKVILLE MD 20855**

**240-276-9317
Fax: 240-276-9327**

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/s/

SAUNDRA T MIDDLETON
06/18/2013

July 3, 2013

The April 24, 2013, Meeting Request was not correctly sent by Sandoz Inc. The Meeting Request instead came from the President of Sandoz directly to Janet Woodcock's office, but not to the OGD document room. As a result, it was not entered into DARRTS when it should have been. Likewise, this Meeting Denied letter was mailed by the Division; it was not entered into DARRTS at that time and it was not mailed by the OGD Document Room.

That Meeting Request and this Meeting Denied letter have since been entered into DARRTS, but have been backdated to reflect the dates that they actually occurred.



ANDA 090218 – Glatiramer Acetate Injection, 20 mg/mL

JUN 4 2013

Sandoz Inc.
Attention: Don DeGolyer, President, North America
506 Carnegie Center Ste 400
Princeton, NJ 08540

Reference Number: OGD #13-0292

Dear Mr. DeGolyer:

This letter is in response to your correspondence dated April 22, 2013. You request a meeting with the Office of Generic Drugs (OGD) to discuss the status of your pending ANDA for generic Glatiramer Acetate Injection, 20 mg/mL (Copaxone®), submitted on December 27, 2007. More importantly, you indicate that you wish to discuss the path forward in the review of the application.

As you know, this is a highly complex product that requires extensive review. Since ANDA 090218 is still currently under review, OGD is unable to grant your meeting request until we have completed review of your amendments dated August 9, and October 27, 2011 and June 13, July 13, September 25, October 26, November 29 and December 10, 2012 and January 20, 2013.

If there are deficiencies noted during the review those will be communicated to you as a complete response. If after you receive a response to your amendment you still would like to meet, OGD can schedule a teleconference to address any questions you may have.

If you have any questions, please call Sandra Middleton at (240) 276-9317. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Craig Wheeler
675 West Kendall Street
Cambridge, MA 02142

Janet Woodcock, M.D., CDER, FDA

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/s/

SAUNDRA T MIDDLETON

06/04/2013

The above letter was sent without this DARRTS signature page on June 4, 2013.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO: (Division/Office) Science Team in the Office of Generic Drugs			FROM: Jing Li	
DATE: 11-9-12	IND NO.	ANDA NO. 90218	TYPE OF DOCUMENT Amendments	DATE OF DOCUMENT 7/20, 8/9/11; 3/23/12
NAME OF DRUG Glatiramer Acetate Injection		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG Peptide	DESIRED COMPLETION DATE 2/9/13
NAME OF FIRM Sandoz Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> OTHER (Specify Below) <input type="checkbox"/> MEETING PLANNED BY _____ <u>Input to the questions raised by Sandoz/Momenta</u>				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER			<input type="checkbox"/> CHEMISTRY <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> PROTOCOL-- BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS Science team, please provide input to the questions raised by Sandoz/Momenta (SM) in ANDA 90218. Thank you.				
SIGNATURE OF REQUESTER Jing Li for Simon Eng			METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

SIMON S ENG
06/03/2013



ANDA 090218

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Sandoz, Inc.
2555 West Midway Blvd.
Broomfield, CO 80020

ATTENTION: Marcy Macdonald
Director Regulatory Affairs

Dear Ms. Macdonald:

Please refer to your Abbreviated New Drug Application (ANDA) dated December 26, 2007, received December 27, 2007, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL.

We also refer to your November 3, 2011, correspondence, received November 8, 2011, requesting review of your proposed proprietary name, Glatopa. We have completed our review of the proposed proprietary name, Glatopa and have concluded that it is acceptable.

The proposed proprietary name, Glatopa will be re-reviewed 90 days prior to the approval of the ANDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 8, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of Generic Drugs (OGD) Regulatory Project Manager, Eunjung Chuh, at (240) 276-8530.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

LAURIE A KELLEY
01/17/2013

CAROL A HOLQUIST
01/17/2013

RECORD OF TELEPHONE CONVERSATION

<p>Teleconference between John Bishop and Jim Anderson of Momenta Pharmaceuticals and Andre Raw and Cecelia Parise of the Office of Generic Drugs</p> <p>Jim Anderson of Momenta Pharmaceuticals contacted Andre Raw about the pending citizen petition submitted by Teva</p> <p>FDA-2012-P-0555 GLATIRAMER ACETATE INJEC 12/1/2012.</p> <p>Andre Raw indicated that we could not discuss issues raised in the CP but the firm could submit information to its application in a gratuitous amendment if they believed that information was necessary for the review of the application. Cecelia Parise also indicated that they could submit comments to the CP docket, also any meeting about the CP would be public and minutes would be put in the docket.</p> <p>The firm was concerned about the several petitions that have been submitted and whether the petition would hold up its approval. Cecelia Parise told Momenta that a response to the current petition was due December 1, 2012.</p> <p>Momenta was also concerned that the questions they were getting in prior deficiency letters were related to scientific issues raised in previous petitions.</p>	<p>DATE 11/9/2012</p>
	<p>ANDA NUMBER 090218</p>
	<p>IND NUMBER</p>
	<p align="center">TELECON</p>
	<p>INITIATED BY MADE _ APPLICANT/ <input checked="" type="checkbox"/> BY SPONSOR TELE.</p>
	<p><input checked="" type="checkbox"/> FDA _ IN PERSON</p>
	<p>PRODUCT NAME Glatiramer</p>
	<p>FIRM NAME Momenta/Sandoz</p>
	<p>NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD John Bishop Jim Anderson</p>
	<p>TELEPHONE NUMBER</p>
<p>SIGNATURE Cecelia M. Parise</p>	

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/s/

SIMON S ENG
11/13/2012



ANDA See Attached

Date: 8/20/2012

Attention:
Department of Regulatory Affairs
SANDOZ
506 CARNAGIE CENTER STE 400
PRINCETON, NJ 08540

RE: Request to Withdraw Applications from the Generic Drug Backlog to Avoid Incurring Backlog Fee

Dear Sir or Madam:

This letter is in reference to your Abbreviated New Drug Applications (ANDAs), included in the attached list, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III), enacted on July 9, 2012, establish a one-time backlog fee for any ANDA that is pending at the US Food and Drug Administration (FDA) on October 1, 2012 and has not received a tentative approval.

FDA is issuing this letter to encourage applicants who have pending ANDAs for which the applicants no longer wish to seek approval to notify FDA of the request to withdraw those ANDAs (see Federal Register Notice Docket Number FDA-2012-N-0879). **Requests for withdrawal should be submitted in writing individually for each ANDA as a “Request for Withdrawal” to the affected ANDA.** A decision to withdraw the ANDA is without prejudice to refileing.

Any ANDA that is not withdrawn by September 28, 2012 will incur the obligation to pay the backlog fee. Payment of backlog fees will be due no later than 30 calendar days after publication in the Federal Register of a notice (to be issued by October 31, 2012) announcing the amount of the backlog fee. Applicants with original ANDAs that fail to pay the backlog fee by the due date will be placed on a publicly available arrears list, and FDA will not receive new ANDAs or supplements submitted by those applicants, or any affiliates of those applicants, until the outstanding fee is paid.

To avoid incurring the backlog fee for an application, you, the applicant, must submit a request to withdraw the application and that request must be received by the FDA on or before **September 28, 2012**. However, to expedite this process, you are encouraged to submit the request by **September 15, 2012**.

You should submit the request to withdraw your applications by standard application submission methods. If an application was submitted via the FDA electronic gateway, a request for withdrawal should be submitted to the application via the gateway. Alternatively, you should send written notification to the ANDA archival file at the following address: Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Document Control Room, Metro Park North VII, 7620 Standish Pl., Rockville, MD 20855.

In addition, please provide electronic confirmation of all ANDAs you wish to withdraw by sending an email to OGDGDUFA@fda.hhs.gov within the timeframe specified above.

For your convenience, a list of pending ANDAs for which we have identified you as the applicant is attached. **However, this list may be incomplete. Therefore, it is important to note that the absence of an ANDA from this list does not exempt that ANDA from incurring a backlog fee. Please verify the list for completeness of all ANDAs you have submitted. Discrepancies should be reported to the email address noted above.**

The GDUFA statute exempts only generic Positron Emission Tomography (PET) products from the user fees. There are no additional exemptions or waivers for GDUFA fees beyond those in the statute.

If you have questions regarding this communication, contact Thomas Hinchliffe at OGDGDUFA@fda.hhs.gov.

Please direct general GDUFA questions to ASKGDUFA@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: Attached List of ANDAs

PENDING ANDAs
(List produced as of 8/20/2012)

ANDA #	Drug Name
	(b) (4)
202609	AZELASTINE HYDROCHLORIDE
203056	BIMATOPROST
90218	GLATIRAMER ACETATE
203563	LEVOLEUCOVORIN CALCIUM
90794	NORGESTIMATE; ETHINYL ESTRADIOL
	(b) (4)

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/s/

WILLIAM P RICKMAN
08/22/2012

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: December 14, 2011
Type of Meeting: Teleconference
Application Number: ANDA 090218
Product Name: Glatiramer Acetate Injection, 20 mg/mL
Sponsor/Applicant Name: Sandoz Inc.

Meeting Chair: Andre Raw, Division Director, Division of Chemistry I
Meeting Recorder: Esther Chuh, Project Manager, OGD

FDA ATTENDEES

Andre Raw, Division Director, Division of Chemistry I
Bing Cai, CMC Team Leader, Division of Chemistry I
Sydney Choi, Science Staff
Robert Lionberger, Science Staff
Sau (Larry) Lee, Science Staff
Huyi Zhang, Science Staff
Esther Chuh, Project Manager

SPONSOR ATTENDEES

Marcy MacDonald, Sandoz Inc, Director, Regulatory Affairs
Nicholas Tantillo, Sandoz Inc, Vice President, Regulatory Affairs
James Anderson, Momenta, Vice President, Drug Product & Analytical Development
John Bishop, Momenta, Senior Vice President, Pharmaceutical Sciences
Claire Coleman, Momenta, Senior Scientist, API
Tanmoy Ganguly, Momenta, Director, Complex Generics
Joe Glajch, Momenta, Director, Analytical Development
Mani Lyer, Momenta, Associate Director, API
Jon Lansing, Momenta, Principal Scientist, Complex Generics
Richard Sachleben, Momenta, Research Fellow, API
Kristina Storey, Momenta, Associate Director, Regulatory Affairs
Aria Tavana, Momenta, Senior Director, API

BACKGROUND

Reference is made to the meeting request submitted to OGD on October 14, 2011 and the teleconference briefing book submitted on November 21, 2011. Reference is also made to the presentation slides (attached) provided by Sandoz for the teleconference.

MEETING OBJECTIVES (as delineated by the sponsor's proposed agenda)**Purpose for this meeting is to:**

- Define Negative Control Strategy
 - Analytical Negative Controls
 - Design Space Negative Controls
 - Application to establishing sameness
- Review Test Plan to Respond to FDA Questions on Negative Controls
- Obtain FDA Feedback on proposed negative control strategy and proposed test plan (Specific questions proposed in Section 5 of the Briefing Book)

DISCUSSION POINTS

** (Normal font for the agency's comments in the internal pre-meeting; italic font in parenthesis for the T-con outcome; the table and page numbers refer to the meeting package)

1. Negative control for biological assays. *(Did not talk about this. There will be separate discussion on the biological assays later.)*

The agency doesn't expect "true" negative controls for biological assays. However, the agency agrees with the proposal that all the negative controls will be analyzed with the biological assays listed in Table 6 and 12. The sponsor will be reminded that the biological assays should be conducted with the sample concentrations within the linear range of the dose response curve, but not on the plateau.

2.

(b) (4)



3.

4.

5.

(b) (4)

Note that the above negative control studies were primarily used to evaluate the sensitivity and specificity of Sandoz's characterization methods with respect to changes in process conditions, thus confirming their use in sameness demonstration. Data obtained from these negative control

studies were not intended for process development. Sandoz would submit process development data separately.

DECISIONS REACHED:

The agency concurs, in general, with the sponsor's proposal on the negative control studies, and additional comments/suggestions are provided to the sponsor as mentioned above. The agency also agrees to accommodate the sponsor's future request of T-cons on specific issues (e.g. biological assays, secondary/tertiary structure, modeling) on a needed basis.

ATTACHMENT:

Following is slides Sandoz provided to OGD on the day of the T- Con:



SANDOZ
MOMENTA



Sandoz / Momenta FDA Meeting
ANDA 090218

14 December 2011



Attendees

Sandoz Inc.

- Emad Alkhawam – Senior Director and Head of Analytical R&D
- Marcy MacDonald – Senior Director, Regulatory Affairs
- Nicholas Tantillo – Vice President, Regulatory Affairs

Momenta Pharmaceuticals, Inc.

- James Anderson, PhD – Vice President, DP & Analytical Development
- John Bishop, PhD – Senior Vice President, Pharmaceutical Sciences
- Claire Coleman, PhD – Senior Scientist, API
- Tanmoy Ganguly, PhD – Director, Complex Generics
- Joe Glajch, PhD – Director, Analytical Development
- Mani Iyer, Ph.D. – Associate Director, API
- Jon Lansing, PhD – Principal Scientist, Complex Generics
- Richard Sachleben, PhD – Research Fellow, API
- Kristina Storey – Associate Director, Regulatory Affairs
- Aria Tavana, PhD – Senior Director, API

Objectives of Meeting

- Define Negative Control Strategy
 - Analytical Negative Controls
 - Design Space Negative Controls
 - Application to establishing sameness
- Review Test Plan to Respond to FDA Questions on Negative Controls
- Obtain FDA Feedback on proposed negative control strategy and proposed test plan
 - Specific questions proposed in Section 5 of the Briefing Book
- Note – Process Design studies will be presented in a subsequent meeting



SANDOZ
MOMENTA



Negative Control Strategy



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/s/

EUNJUNG E CHUH
12/22/2011

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: August 11, 2011 1:30 PM – 3:30 PM

Meeting Location: MPN IV Conference Room 4A

Application Number: ANDA 090218

Product Name: Glatiramer Acetate Injection, 20 mg/mL

Sponsor/Applicant Name: Sandoz Inc.

Meeting Chair: Lawrence Yu, Acting Deputy Director for Science and Chemistry

Meeting Recorder: Esther Chuh, Project Manager, OGD

FDA ATTENDEES

Lawrence Yu, Acting Deputy Director for Science and Chemistry

Paul Schwartz, Acting Division Director, Division of Chemistry I

Andre Raw, Acting Deputy Division Director, Division of Chemistry I

Bing Cai, CMC Team Leader, Division of Chemistry I

Eugene Schaefer, CMC Reviewer, Division of Chemistry I

Robert Lionberger, Science Staff

Sau (Larry) Lee, Science Staff

Rebecca Brummit, Science Staff

Zhang, Xinyuan, Science Staff

Huyi Zhang, Science Staff

Esther Chuh, Project Manager

SPONSOR ATTENDEES

Marcy MacDonald, Sandoz Inc, Director, Regulatory Affairs

Nicholas Tantillo, Sandoz Inc, Vice President, Regulatory Affairs

Emad Alkhawam, Sandoz Inc, Senior Director and Head of Analytical R & D

James Anderson, Momenta, Vice President, Drug Product & Analytical Development

John Bishop, Momenta, Senior Vice President, Pharmaceutical Sciences

Aria Tavana, Momenta, Senior Director, API

Kei Kishimoto, Momenta, Vice President, Translational Research

Ishan Capila, Momenta, Director, Discovery

Nic Scalfarotto, Momenta, Vice President, Regulatory Affairs

BACKGROUND

Reference is made to the original ANDA submitted on December 26, 2007 and to the CMC amendments dated October 16, 2009, December 9 and 17, 2010; January 14, and March 2, 2011; and to the Meeting Request submitted on May 10, 2011. Reference is also made to the Meeting Briefing package submitted to OGD on July 11, 2011 and to the presentation slides (attached) used during the meeting. Reference is also made to the CMC deficiencies issued by this office on September 15, 2008; February 14, June 22, and July 29, 2011. Meeting request was granted by this office on June 7, 2011.

MEETING OBJECTIVES (as delineated by the sponsor's proposed agenda)

Purpose for this meeting is to:

- Discuss potential for enhancing responses and interaction efficiencies between Sandoz / Momenta and FDA
- Propose overall strategy and criteria for determination of sameness on the Biological and Immunological Testing and Physicochemical Characterization
- Communicate improvements to the Drug Substance manufacturing process
- Obtain clarification on biological and CMC questions received in June 23, 2011 Major Deficiency

DISCUSSION POINTS

Biological and Immunological Testing Proposal

- The Agency concurred with the applicant's proposal on the biological and immunological testing strategy in general, and encouraged the applicant to explore and adopt additional bioassays pertaining mechanisms of action in order to thoroughly demonstrate the equivalence in biocharacterization.
- The Agency recommended using negative controls to demonstrate the specificity and sensitivity of these bioassays and provide the relevant method qualification information to show that these bioassays are appropriate for the intended purposes.

Chemical Characterization

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- The applicant raised the issues of [REDACTED] (b) (4). The Agency suggested [REDACTED] (b) (4).
- The applicant stated that there is no [REDACTED] (b) (4). The Agency asked for additional information to confirm this statement.
- Regarding depolymerization step, [REDACTED] (b) (4).

Administrative Proposals

- The Agency is open to granting meetings and t-cons in the future to further discuss the application as needed, and suggested that the applicant should focus on the API sameness issue by conducting additional studies as discussed above.
- The Agency concurred with the applicant's proposal to group the responses in specific areas or topics, and suggested to focus on answering the deficiencies related to the API sameness.

DECISIONS REACHED:

The applicant needs to focus on the API sameness issues, conduct and submit additional studies to demonstrate the sameness with RLD.

ATTACHMENT:

Following is Sandoz's Meeting Minutes with OGD's comments.



Application: ANDA 090218 (Glatiramer Acetate Injection, 20 mg/mL)

Meeting Attendees: Sandoz US Inc. (Sponsor)
Momenta Pharmaceuticals, Inc. (on behalf of Sponsor)
Food and Drug Administration

Meeting Date / Time: August 11, 2011, 1:30 – 3:30 pm EST

Meeting Location: FDA: 7500 Standish Place
Rockville, MD 20855

Meeting Goals

- Discuss potential for enhancing responses and communication efficiencies between Sandoz / Momenta and FDA
- Propose overall strategy and criteria for determination of sameness
- Communicate improvements to the Drug Substance manufacturing process
- Obtain clarification on biological and CMC questions received in June 23, 2011 Major Deficiency

Attendees: Sandoz US Inc.

Emad Alkhawam, PhD – Senior Director and Head of Analytical R&D
Marcy Macdonald – Director, Regulatory Affairs
Nicholas Tantillo – Vice President, Regulatory Affairs

Attendees: Momenta Pharmaceuticals, Inc.

James Anderson, PhD – Vice President, DP & Analytical Development
John Bishop, PhD – Senior Vice President, Pharmaceutical Sciences
Ishan Capila, PhD – Director, Discovery
Tanmoy Ganguly, PhD – Director, Complex Generics
Joe Glajch, PhD – Director, Analytical Development
Jon Lansing, PhD – Principal Scientist, Complex Generics
Richard Sachleben, PhD – Research Fellow, API
Nic Scalfarotto, DVM – Vice President, Regulatory Affairs
Aria Tavana, PhD – Senior Director, API
Ganesh Venkataraman, PhD – Chief Scientific Officer, Senior Vice President, Research; Co-Founder

Attendees: FDA

Lawrence Yu: Acting Deputy Director for Science and Chemistry
 Paul Schwartz, Acting Division Director, Division of Chemistry I
 Andre Raw, Acting Deputy Division Director, Division of Chemistry I
 Eugene Schaefer, CMC Reviewer, Division of Chemistry I
 Bing Cai, CMC Team Leader, Division of Chemistry I
 Robert Lionberger, Science Staff
 Sau Lee, Science Staff
 Rebecca Brummit, Science Staff
 Xinyuan Zhang, CMC Reviewer
 Huyi Zhang, Science Staff
 Ester Chuh, Project Manager

Introductory Discussion

Following introductions, L. Yu (FDA) stated that the Agency was not prepared to respond to specific questions. He indicated that this would be an informational meeting, after which there would be a discussion regarding administrative issues.

E. Schafer (FDA) indicated that he had performed all the CMC reviews of the ANDA covering Drug Substance and Drug Product.

J. Bishop (MNTA) provided the meeting agenda and objectives then introduced Sandoz / Momenta's (SDZ-MNTA) proposed framework for evaluating sameness.

1. FDA was in general agreement that there were too many species present in Copaxone to equate its assessment to that of Enoxaparin Sodium. ~~An evaluation of fragments was not considered to be a useful exercise.~~

An evaluation of individual polymer specie, such as sequencing, was not considered to be practical.

Biology and Immunology Discussion

G. Venkataraman (MNTA) presented the SDZ-MNTA section on Biology and Immunology.

1. A. Raw (FDA) stated that a general question existed regarding negative controls for the bio-assays. S. Lee (FDA) concurred and stated that this was an issue, in general, for all of the methods.
 - a. SDZ-MNTA must demonstrate the sensitivity of their methods via use of negative controls.
 - b. The Agency emphasized need to demonstrate method sensitivity to distinguish between glatiramer-like compounds (i.e. that glatiramer-like compounds are negative controls).
2. E. Schaefer (FDA) stated that SDZ-MNTA approach to bio-characterization was considered to be a good proposal.

It is acknowledged that EAE is not performed as a release test, but rather a characterization test

- a. ~~The concept of not performing EAE was found to be acceptable~~, at this time, although the FDA wanted to understand why specific methods were or were not selected. Two specific examples were cited: (1) Th17 vs Th1 or (2); CD4 vs CD8.
 - b. SDZ-MNTA was requested to provide justification for the choice of specific bio-characterization methods/tests, including comparison to alternative assays reported in the literature on MS. The Agency may request additional assay types if it is deemed necessary.
3. E. Schaefer noted that all of the proposed methods focused on peripheral activity and that no work was presented relating to cell / mechanisms that occur after crossing the blood brain barrier. It was suggested that SDZ-MNTA evaluate the impact of peripheral vs CNS activity of Glatiramer Acetate (GA) on MS biology.
- a. G. Venkataraman noted that goal was to use bio-characterization assays to demonstrate pharmaceutical equivalence of GA to RLD, not to clarify the mechanism for GA efficacy.
4. E. Schaefer stated that FDA requested that the biological tests be validated. These tests were found to be acceptable in general, but it was suggested that there may be others worth considering. It was admitted that this was not typical, but that the Agency would want to have available validation reports for the biological methods.
- a. It was suggested that SDZ-MNTA provide method validation/qualification to demonstrate sensitivity and reliability of the proposed bio-characterization methods. It is encouraged to explore and adopt additional bioassays pertaining possible MOAs while it is acknowledged that these exercises are not aimed to investigate the MOAs.
 - b. Specifically mentioned were: specificity, linearity, accuracy and precision studies.
5. ~~FDA agreed that the performance of MOA studies was not required and that the general plan, which included not conducting EAE, was acceptable.~~ However, FDA reiterated that a justification of the plan was required.

Mathematical Model Discussion

Please confirm [REDACTED] (b) (4)

1. FDA indicated that they understood how modeling had been used as a predictor of what should be measured. An understanding was expressed, by the Agency, that modeling of general features as one unit was being performed (i.e. - [REDACTED] (b) (4) and other termination events as one factor).
- a. The Agency review team accepted SDZ-MNTA position on the role of the mathematical model as a guidance tool.
 - b. L. Yu indicated that the Agency believes that modeling is critical for demonstrating sameness, and that FDA would like confidence that the model is, in fact, expressing all of the factors that need to be measured.

2. FDA expects the model to be an independent predictor of what is important to measure. To that end, FDA suggested verification of the model via examination of **parameters** outside of our design space (specifically the ^{(b) (4)} conditions and temperature differences). These kinetic parameters should be determined experimentally before adopted in the kinetic modeling
3. A. Raw asked that the ^{(b) (4)} **kinetics** in ^{(b) (4)} be modeled.

CMC Discussion

1. (b) (4)
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.

15.

(b) (4)

16.

17.

18.

Administrative Discussion

1. L. Yu reiterated that OGD would need to be convinced that equivalence existed between the RLD and the Sponsor’s materials.. Demonstrating equivalence would facilitate further discussion and review within FDA. L. Yu indicated that further communication and discussion between the Agency and the Sponsor would be welcome.
2. L. Yu suggested that the focus be placed on demonstrating sameness of the Drug Substance materials – specifically polymerization and other steps of the process. FDA would like to have identification of structures that are sensitive to process conditions and then demonstration of sameness between the Sponsor’s product and RLD.
3. M. Macdonald (SDZ) proposed periodic meetings on specific topics pertaining to the discussions today and working with the Agency staff to determine the process for these meetings. FDA was receptive to this idea. FDA agreed to scheduling additional meetings on specified topics focused on establishing equivalence and other issues.
 - a. SDZ-MNTA suggested that there would be 4 to 5 sub-units developed to address FDA questions. Specific areas could include (b) (4), bio-assays. FDA indicated that would be acceptable. A. Raw suggested that we focus on (b) (4) for the time being.
4. N. Tantillo (SDZ) further proposed a more flexible deficiency response process, suggesting bundling of response items based on timing of completion or topic. FDA also agreed to grouping and submitting responses that focused on targeted areas.

5. E Schaefer asked for a streamlined response document with reference to an updated eCTD document. He indicated that each table (even when presented in multiple sections) required detailed review. He suggested that the data be kept to a single source or be presented a limited number of times.

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/s/

EUNJUNG E CHUH
09/30/2011

QUALITY DEFICIENCY – MAJOR

ANDA 090218



OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Sandoz, Inc.

TEL: 303-438-4599

ATTN: Marcy Macdonald

FAX: 303-438-4600

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 26, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL.

Reference is made to your amendments dated October 16, 2009; and April 30, December 9, and December 17, 2010; and January 14, and March 2, 2011

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MAJOR AMENDMENT / RESPONSE TO INFORMATION REQUEST** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

**Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855**

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THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090218

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Glatiramer Acetate Injection, 20 mg/mL

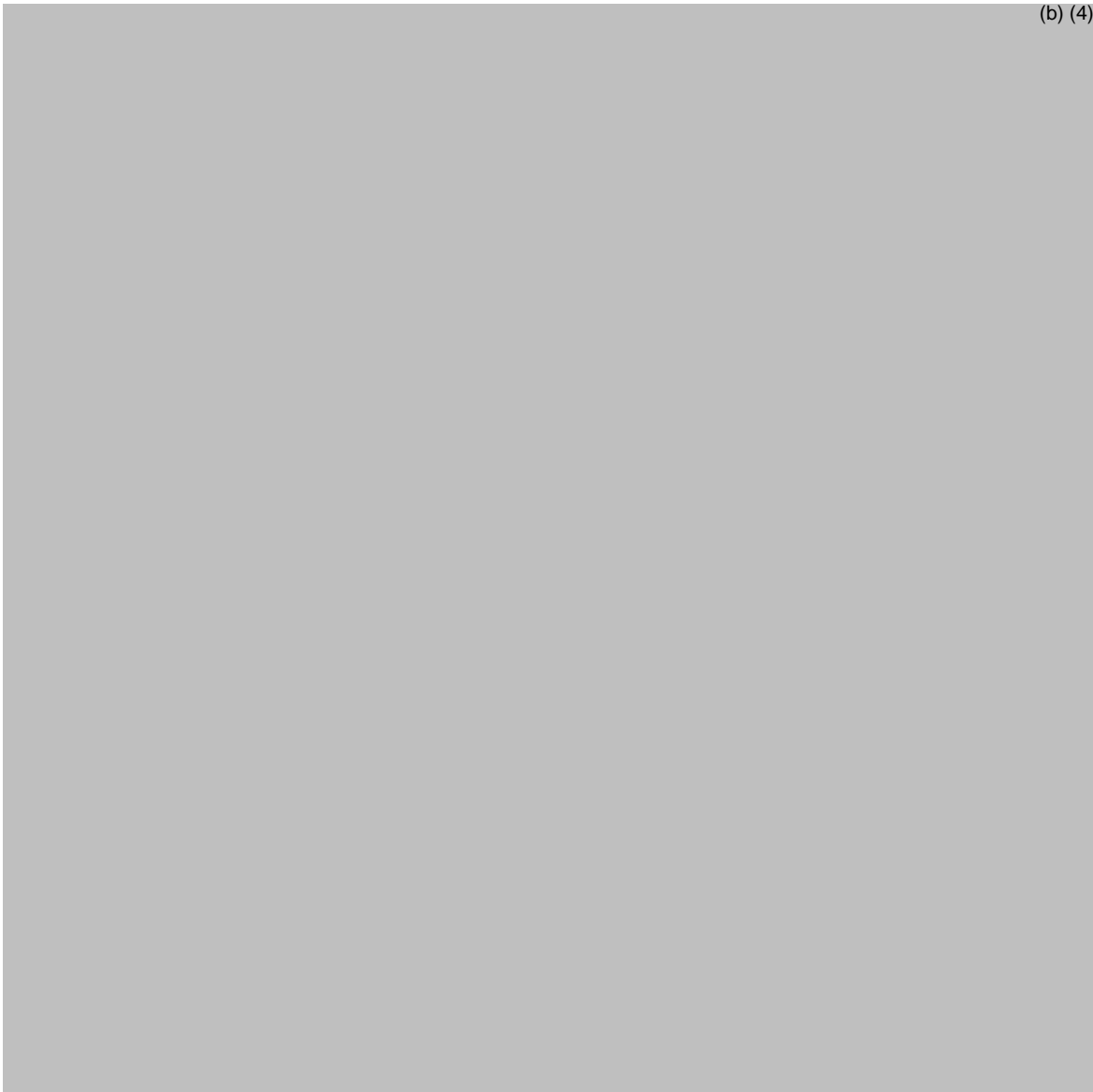
Review of all information that has been submitted for the drug substance until now has been completed. Review of drug product information is continuing. Further deficiencies, if any, will be communicated separately.

The deficiencies presented below represent a continuation of the MAJOR deficiencies that we communicated to you on February 14, 2011.

A. Deficiencies:

- 1.
- 2.
- 3.
- 4.
- 5.

(b) (4)



Following this page, 12 pages withheld in full - (b)(4)

52.

53.

54.

55.

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
 2. An acceptable compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.
 3. Review of your mathematical models is continuing. Additional deficiencies, if any, will be communicated separately.

Sincerely,

{See appended electronic signature page.}

Paul Schwartz, Ph.D.
Acting Director,
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BING CAI
06/22/2011
For Paul Schwartz

MEETING DATE: May 13, 2011
DRUG NAME: Glatiramer Acetate Injection
ANDA 90-218 (Sandoz/Momenta)
TYPE OF MEETING: Teleconference
MEETING RECORDER: Sau (Larry) Lee

ATTENDEES: John Bishop, Momenta
Ishan Capila, Momenta
Andre Raw, Office of Generic Drugs (OGD)
Sau (Larry) Lee, OGD

SUMMARY: Dr. Bishop and Dr. Capila (Momenta) informed Dr. Andre and Dr. Lee (OGD) by telephone on May 13, 2011 that Sandoz/Momenta recently submitted a meeting request package to OGD and wished to have a face-to-face meeting to discuss with OGD regarding issues related to drug substance sameness of glatiramer acetate. Dr. Andre and Dr. Lee acknowledged that they have received the meeting request package, and that OGD will review the package to determine whether a face-to-face meeting will be warranted according to OGD's general practice for granting a face-to-face meeting.

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/s/

EUNJUNG E CHUH
05/15/2011

Record of Telephone Conversation

<p>Reference is made to the Meeting Request submitted on March 11, 2011. Sandoz was contacted to notify that their request is denied.</p> <p>In order to determine the [REDACTED] (b) (4), OGD requested that Sandoz submit their proposed [REDACTED] (b) (4) [REDACTED] (b) (4) for our review. Sandoz agreed and informed us that it may take 3-4 months for the submission.</p>	<p style="text-align: center;">Date: 4/28/11</p>
	<p style="text-align: center;">ANDA Number: 090218</p>
	<p style="text-align: center;">Product Name: Glatiramer Acetate Injection, 20mg/mL</p>
	<p style="text-align: center;">Firm Name: Sandoz Inc.</p>
	<p style="text-align: center;">Firm Representative:</p> <p>Sandoz: -Marcy Macdonald, Director, Reg Affairs</p>
	<p style="text-align: center;">Phone Number: 303-438-4599</p>
	<p style="text-align: center;">FDA Representative:</p> <p>- Andre Raw, Acting Deputy Division Director, DCI -Esther Chuh, Project Manager</p>

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/s/

EUNJUNG E CHUH
04/28/2011

QUALITY DEFICIENCY – MAJOR

ANDA 090218

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



APPLICANT: Sandoz, Inc.

TEL: 303-438-4599

ATTN: Marcy Macdonald

FAX: 303-438-4600

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 26, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL.

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The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ___ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MAJOR AMENDMENT / RESPONSE TO INFORMATION REQUEST** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

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CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 090218

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Glatiramer Acetate Injection, 20 mg/mL

This review has been focused on Section S.3.1 Elucidation of Structure, although some other sections have been partially reviewed. Review of other parts of the ANDA is continuing. Further deficiencies, if any, will be communicated separately.

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1.

(b) (4)

2.

3.

4.

5.

6.

30.

(b) (4)

31.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated separately.
2. An acceptable compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.

Sincerely,

{See appended electronic signature page.}

Paul Schwartz, Ph.D.
Acting Director,
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

BING CAI
02/14/2011
For Paul Schwartz

Record of Telephone Conversation

Reference is made to the Teleconference held on November 23, 2010, and the T- Con Memo filed in DARRTS on December, 3, 2010, where OGD requested the Sandoz/Momenta Java Codes and other associated files. Reference is also made to the email correspondences between Sandoz and FDA eSUB team and also between eSUB and this office (see attachment).

On 12/13/10 firm was contacted to request the firm to submit our requested file in ASCII format with .txt file extension.

Firm said they will contact Momenta so see if they can meet our request.

Date:
12/13/2010

ANDA Number:
090218

Product Name:
Glatiramer Acetate
Injection, 20mg/mL

Firm Name:
Sandoz Inc.

Firm Representative:

Sandoz:
-Jean Domenico
Manager, Reg Affairs

Phone Number:
303-438-4242

FDA Representative:
- Rebecca Brummitt
Science Staff
-Esther Chuh
Project Manager

Signatures:

Rebecca Brummitt

Esther Chuh

ATTACHMENT:

From: Cai, Bing
Sent: Saturday, December 11, 2010 9:34 AM
To: Gooding, Valerie
Cc: Warfield, Douglas; Raw, Andre; Brummitt, Rebecca *; Chuh, Esther; CDER ESUB
Subject: RE: esub question

Hello, Dear Valerie,

Thank you very much for your help.

Bing

From: Gooding, Valerie
Sent: Friday, December 10, 2010 1:22 PM
To: Cai, Bing
Cc: Warfield, Douglas; Raw, Andre; Brummitt, Rebecca *; Chuh, Esther; CDER ESUB
Subject: RE: esub question

Dear Bing,

It was discussed with Doug that sponsor providing the instruction file in .pdf extension is acceptable from an ESUB standpoint however, the approval of all the other file extensions which are datasets related, was deferred to the edata team. We do not have any further question regarding this submission.

Regards,

Valerie Gooding

Regulatory Information Specialist, Electronic Submission Support, CDER (301-796-0902)

From: Cai, Bing
Sent: Friday, December 10, 2010 8:44 AM
To: CDER ESUB
Cc: Warfield, Douglas; Raw, Andre; Brummitt, Rebecca *; Chuh, Esther
Subject: FW: esub question

Hello, Dear ESUB team,

We have some discussion with Mr. Douglas Warfield. He has provided us very useful information and recommendation.

Please let us know if you have any further questions regarding this submission.

We will inform Sandoz to follow the instructions provided by Douglas.

Thanks,

Bing

From: Warfield, Douglas
Sent: Friday, December 10, 2010 8:27 AM
To: Brummitt, Rebecca *
Cc: Raw, Andre; Cai, Bing; Gooding, Valerie
Subject: RE: esub question

As we discussed in our phone conversation on December 10, 2010, the submission of the programs (code) to support your risk assessment of the Sandoz Kinetic Monte-Carlo modeling process for manufacturing glatiramer acetate drug substance in the ANDA 09218 submission **is acceptable provided the sponsor adds the .txt file extension to the programs**. We would be glad to provide any additional support for your team in sponsor correspondence/meetings as well.

If you have any further questions, please feel free to send an email to cdcr-edata@fda.hhs.gov.

Best regards,

Douglas Warfield
Regulatory Information Specialist
Office of Business Informatics
CDER, FDA
301-796-7609

From: Brummitt, Rebecca *
Sent: Thursday, December 09, 2010 12:24 PM
To: Warfield, Douglas
Cc: Raw, Andre; Cai, Bing
Subject: FW: esub question

Hi Douglas,

Based on your recommendations and the conversation you had with Bing Cai this morning, we plan to request that Sandoz submit all files in ASCII format. The file extensions they would like to submit are given below.

.pdf (instruction file)
.res (text files containing examples of program outputs)
.txt (text files containing input parameters for some of the programs)
.java (text files containing Java code)
.class (compiled Java code, executable only through a Java Virtual Machine, i.e. double-clicking won't do it)
.bat (text file, but executable via MSDOS command window or by double-clicking)
All except those with the .class extension are already in a text (ASCII) format, and we will have them convert the class files to ASCII format as well.

Please verify that this will be okay before we make this request of Sandoz.

Thank you for your help.

Rebecca

From: Cai, Bing
Sent: Thursday, December 09, 2010 9:16 AM
To: Raw, Andre

Cc: Brummitt, Rebecca *; Chuh, Esther
Subject: FW: esub question

From: Warfield, Douglas
Sent: Thursday, December 09, 2010 9:16 AM
To: Cai, Bing
Cc: Gooding, Valerie
Subject: RE: esub question

For the submission for [ANDA 90-218](#), the sponsor (Sandoz) should submit program files in ASCII format, consistent with the [Study Data Specifications](#) (pg. 5). The PDFs of the programs are not required. The sponsor should locate the files under the [m3, m4, or m5]\datasets\[studyname]\analysis\programs directory, again per the [Study Data Specifications](#) (pg. 8). Program files (.sas, .json, .vbs, etc.) that are viewable as ASCII formatted files are acceptable.

The [Study Data Specifications](#) require the sponsor to submit all datasets in SAS Transport (v5) files. The sponsor should locate the files under the [m3, m4, or m5]\datasets\[studyname]\[analysis, tabulations, or listings]\datasets directory, again per the [Study Data Specifications](#) (pg. 8).

The [Study Data Specifications](#) provide the most conducive data content definition and structure for the review team, although this may vary based on the submission and reviewing division (pg. 2). The review team assigned to the submission determines the acceptability. The industry guidance provided includes encouragement to follow this best practice noted in the [Study Data Specifications](#), "prior to submission, sponsors should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset and the organization of the data within the file" (p. 2).

If you have any further questions, please feel free to send an email to cdler-edata@fda.hhs.gov.

Thanks.

Douglas Warfield
Regulatory Information Specialist
Office of Business Informatics
CDER, FDA
301-796-7609

From: Cai, Bing
Sent: Thursday, December 09, 2010 08:12 AM
To: Hussong (Ventura), Virginia
Cc: Raw, Andre; Brummitt, Rebecca *; Chuh, Esther
Subject: FW: esub question

Hello, Ginny,

I like to talk to you today regarding the submission of the ANDA 90-218.

I am working from home today.

You may call me at [REDACTED] (b) (6)

We need to have this issues resolved ASAP.

Thanks,

Bing

From: Robinson, Constance
Sent: Wednesday, December 08, 2010 5:12 PM
To: Cai, Bing; Hussong (Ventura), Virginia
Cc: Raw, Andre; Chuh, Esther; Brummitt, Rebecca *; CDER ESUB
Subject: RE: esub question

Hello,

Since I'll be out of the office the next two days, please include esub@fda.hhs.gov since the email account is monitored by our entire team.

Thank you,

Connie

From: Cai, Bing
Sent: Wednesday, December 08, 2010 5:05 PM
To: Hussong (Ventura), Virginia
Cc: Raw, Andre; Robinson, Constance; Chuh, Esther; Brummitt, Rebecca *
Subject: FW: esub question

Ginny, Would you contact me regarding this matter? We need this information from firm ASAP.

Bing

From: Robinson, Constance
Sent: Wednesday, December 08, 2010 4:54 PM
To: Chuh, Esther
Cc: CDER ESUB; Cai, Bing; Hussong (Ventura), Virginia
Subject: RE: esub question

Hello Esther,

For security and compliance purposes, they shouldn't submit those files at all. I'm including my team leader, Ginny Hussong, in my reply to you for her advice or recommendations.

Best Regards,

Connie Robinson, RAC, PMP

Regulatory Information Specialist
Office of Business Informatics (OBI)
Division of Regulatory Review Support (OBI - DRRS), CDER

U.S. Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 1105
Silver Spring, MD 20993
Phone: (301) 796-1065
Fax: (301) 796-9886
Constance.Robinson-Kuiperi@fda.hhs.gov

From: Chuh, Esther
Sent: Wednesday, December 08, 2010 4:45 PM
To: Robinson, Constance
Cc: CDER ESUB; Cai, Bing
Subject: RE: esub question

Hello Connie,

Would it be acceptable if the firm submits the information in a CD?

Thank you,
Esther

From: Robinson, Constance
Sent: Tuesday, December 07, 2010 10:11 AM
To: Chuh, Esther
Cc: CDER ESUB
Subject: FW: esub question

Hello Esther,

I left you a voicemail regarding the inquiry below. We (CDER-OPI-OBI-DRRS-eSST) received the inquiry below. As per the specifications, submitting software programs is not allowed for security and archiving reasons. If your request pertained to data, the programs should be requested in the format allowed per data specifications (.txt and .pdf files).

Was there a specific reason why you requested a software program be sent by the sponsor?

Best Regards,

Connie Robinson, RAC, PMP

Regulatory Information Specialist
Office of Business Informatics (OBI)
Division of Regulatory Review Support (OBI - DRRS), CDER
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 1105
Silver Spring, MD 20993
Phone: (301) 796-1065
Fax: (301) 796-9886
Constance.Robinson-Kuiperi@fda.hhs.gov

To help ensure that you receive the most prompt response to your inquiry, please always include esub@fda.hhs.gov if you have electronic submission questions to CDER.

For the FDA CDER eCTD web page, please visit
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>

From: (b) (6)@sandoz.com [mailto:(b) (6)@sandoz.com]
Sent: Monday, December 06, 2010 5:13 PM
To: CDER ESUB
Subject: esub question

Jean Domenico/GX/Novartis

To (b) (6)/GX/Novartis@PH
cc

12/06/2010 02:35 PM

Subject esub question

We are electronically submitting a software program, along with an eCTD sequence to one of our applications. Can this software be received by your Document Control Room for this submission if submitted on two CDs or two separate ESG submissions? In addition, would it be preferred to have two CDs - one containing the software program and the other containing the eCTD sequence information (i.e. cover letter and 356h). If not, please communicate the preferred method for filing such an amendment which is not part of the XML backbone.

We are submitting this software information per the question of FDA (Esther Chu's group).

If you have any questions, please don't hesitate to contact me.

Jean Domenico
Manager, Regulatory Affairs

Sandoz Inc.
2555 West Midway Boulevard
Broomfield, CO 80020
USA
Phone: +1 303 438 4242
Fax: +1 303 438 4600
Cell: +1 (b) (6)
Email : jean.domenico@sandoz.com

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/s/

EUNJUNG E CHUH
12/20/2010

Record of Telephone Conversation

<p>On 11/22/2010, OGD requested a teleconference with Sandoz, specifically requesting the presence of their staff involved in the computer programming and development of the mathematical models that are used to describe the polymerization process for the formation of the glatiramer acetate. The purpose of the meeting was to request the Sandoz/Momenta Java codes and other associated files for the Kinetic Monte-Carlo modeling of the polymerization, depolymerization with uniform cleavage, depolymerization with biased cleavage, and deprotection steps of the process for manufacturing glatiramer acetate drug substance.</p>	<p style="text-align: center;">Date: 11/23/2010</p>
<p>Following are the conversations captured during the meeting:</p>	<p style="text-align: center;">ANDA Number: 090218</p>
<p>OGD: We are doing an in-depth analysis of the model and in order to fully evaluate the model presented, we need the Java codes and other associated codes and files. OGD specifically requested the files that are described in Appendix B: Process signatures in models of Glatiramer Acetate. All files to describe the polymerization, depolymerization, and deprotection models in the entire section are needed except the Runge-Kutta portion at the beginning of the polymerization section.</p>	<p style="text-align: center;">Product Name: Glatiramer Acetate Injection, 20mg/mL</p>
<p>Sandoz stated the following key attributes of the models and inquired how OGD intends to use the files:</p>	<p style="text-align: center;">Firm Name: Sandoz Inc.</p>
<p style="padding-left: 40px;">Model is used as a supportive tool to support the knowledge of the process signatures that need to be experimentally tested in the drug substance.</p>	<p>Firm Representative:</p> <p>Sandoz:</p> <ul style="list-style-type: none"> -Marcy Macdonald, Director, Reg Affairs - (b) (6), Project Lead <p>Momenta:</p> <ul style="list-style-type: none"> -John Bishop, Sr. VP, Pharm. Sci. - (b) (4) Consultant -Ishan Capila, Associate Director, Analytical Research -Ganesh Venkataraman, CSO & Sr. VP, Research -Jim Roach, Chief Medical Officer and Acting Head of Regulatory Affairs
<p style="padding-left: 40px;">As a set of analytical methods to understanding the polymerization/depolymerization process</p>	<p style="text-align: center;">Phone Number: 303-438-4599</p>
<p>OGD acknowledged and stated that we understand the key attributes of the model and stated that the request for the codes is to better understand the model for its intended use. Our purpose is to make sure that the model is robust. Some of the aspects we want to test are the hypothesis and the assumptions, parameters, sensitivity, and that the model is reproducible.</p>	<p>FDA Representative:</p> <ul style="list-style-type: none"> - Andre Raw, Acting Deputy Division Director, Division of Chemistry I - Larry Lee, Science Staff - Bing Cai, Team Leader, Division of Chemistry I - Eugene Schaefer, CMC Reviewer, Division of Chemistry I - Rebecca Brummitt, Science Staff - Esther Chuh, Project Manager
<p>Sandoz stated that some aspects of the model are clear to see but other aspects would not be clear to analyze and that the model cannot recreate certain aspects and that it is not intended to capture the fine details.</p>	
<p>OGD acknowledged the limitations of the model and assured that the codes will be analyzed with the understanding of their limitations.</p>	
<p>In addition to the requested files, OGD requested the initiation and elongation rate constants at all temperatures examined experimentally.</p>	

<p>Sandoz agreed to send the requested files and also the exc. file and experimental rate constant results within the next 7-14 days and inquired how this will be incorporated with the review process of the ANDA.</p> <p>OGD stated that the mathematical aspect is interrelated to the CMC portion, and they are under simultaneous review. Sandoz can inquire regarding the status of the entire application with the project manager at a later date.</p> <p>Sandoz asked if they could request for a face to face meeting to discuss their ANDA and OGD responded that the possibility can be discussed at a later date after OGD issues the CMC comments, if any.</p>	<p>Signatures :</p> <p>Andre Raw Larry Lee Bing Cai Eugene Schaefer Rebecca Brummitt Esther Chuh</p>
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/s/

EUNJUNG E CHUH
12/03/2010

Meeting Request Denied.

Firm was notified with below response:

From: West, Robert L
Sent: Monday, February 01, 2010 11:16 AM
To: Chuh, Esther
Cc: Yu, Lawrence; Cai, Bing; Buehler, Gary J; Read, David T; Parise, Cecelia M
Subject: FW: ANDA 90-218 Glatiramer Acetate Injection 20 mg/mL

Esther:

I think we should inform Sandoz that it is not appropriate to meet on Glatiramer at this time. We have not made sufficient progress on the review to provide an accurate assessment.

The office will address Sandoz's eligibility for exclusivity at the time of approval.

I'm uncertain as to what we should say about immunogenicity. Others can advise on this point.

Bob

From: srinivasa_s.rao@sandoz.com [mailto:srinivasa_s.rao@sandoz.com]
Sent: Wednesday, January 27, 2010 11:39 AM
To: West, Robert L
Subject: RE: ANDA 90-218 Glatiramer Acetate Injection 20 mg/mL

Bob,

Sorry for the delayed response.

We would like to discuss immunogenicity and bioequivalence topics in addition to eligibility for an exclusivity. As stated in our meeting request, FDA is applying increased emphasis to the assessment of the potential immunogenicity of drug products. Moreover, a recent Citizen's Petition submitted by Teva Neuroscience [FDA-2009-P-0555] discusses the potential immunogenicity of Glatiramer Acetate Injection. However, the assessment of potential immunogenicity is not currently a regulatory requirement for ANDA applications and, to date, FDA has not requested immunogenicity information as part of its review of ANDA 90-218. Sandoz has proposed a prospective discussion on this topic to facilitate the timely approval of ANDA 90-218. Also, any insight on exclusivity prior to our face-to-face meeting would be appreciated, as this would help to focus our meeting towards these science-related topics.

Best regards,

Srinivasa S. Rao, M.Pharm., MS, PharmD
Director, Regulatory Affairs
Sandoz Inc.

Sandoz Inc.
506 Carnegie Center, Suite 400
Princeton, NJ 08540
USA
Phone: +1 609 6278885
Fax: +1 609 3952792
Cell: +1 (b) (6)
Email : srinivasa_s.rao@sandoz.com

"West, Robert L" <Robert.West@fda.hhs.gov>

To srinivasa_s.rao@sandoz.com

cc

01/22/2010 12:50 PM

Subject RE: ANDA 90-218 Glatiramer Acetate Injection 20 mg/mL

Please respond to Robert.West@fda.hhs.gov

Yes, I'm working on it.

Is the primary issue whether or not Sandoz will lose its eligibility for exclusivity if the agency is unable to issue a T/A letter within 30 months? If so, I may be able to resolve this without needing a meeting.

Bob

From: srinivasa_s.rao@sandoz.com [mailto:srinivasa_s.rao@sandoz.com]
Sent: Friday, January 22, 2010 12:38 PM
To: West, Robert L
Subject: ANDA 90-218 Glatiramer Acetate Injection 20 mg/mL

Bob,

Happy New Year

Product: Glatiramer Acetate Injection 20 mg/mL
ANDA#: 90-218

A face-to-face meeting request was sent to the Agency on December 14, 2009. Please see attached for your reference. A follow-up call was placed to the project Manager Esther Chu dated 1/20/2010. As per Esther no decision was made by the Agency in reference to this meeting request.

Could you please expedite this request. Any help is greatly appreciated.

Best regards,

Srinivasa S. Rao, M.Pharm., MS, PharmD
Director, Regulatory Affairs
Sandoz Inc.

Sandoz Inc.
506 Carnegie Center, Suite 400
Princeton, NJ 08540
USA
Phone: +1 609 6278885
Fax: +1 609 3952792
Cell: +1 (b) (6)
Email : srinivasa_s.rao@sandoz.com

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- ANDA-90218	----- GI-1	----- SANDOZ INC	----- GLATIRAMER ACETATE

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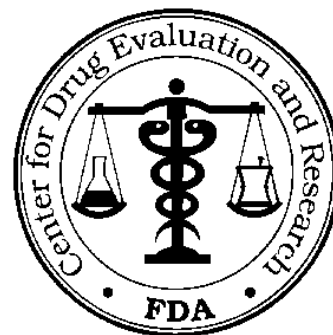
/s/

EUNJUNG E CHUH
03/04/2010

Telephone Fax

ANDA 90-218

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
Angela.payne@fda.hhs.gov



TO: Sandoz

TEL: 609-627-8885

ATTN: Srinivasa Rao

FAX: 609-395-2792

FROM: Mrs. Angela Payne

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection.

Pages (including cover): 3

SPECIAL INSTRUCTIONS:

See attached labeling comments.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

**REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH
Superceds TAP1**

ANDA Number: 90-218

Date of Submission: Jul 07, 2008

Applicant's Name: Sandoz Inc.

Established Name: Glatiramer Acetate Injection 20 mg/mL, Single Use Syringe

Labeling Deficiencies:

1. **CONTAINER** (1 mL): Revise the expression of strength to 20 mg/mL rather than just 20 mg. Please also submit a diagram of your syringe noting calibrations.
2. **BLISTERS (1s)**- Your labeling says protect from light. If the blister does not protect the pre-filled syringe from light we encourage you to add "Retain in carton".
3. **CARTON** (30X- 1 mL): Delete the ##s seen in the NDC.
4. **INSERT**: Satisfactory in draft.
5. **PATIENT LEAFLET**: Satisfactory in draft.

Revise your labels and labeling, as instructed above, and submit final printed electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - <http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

John Grace
12/10/2008 11:25:30 AM
for Wm Peter Rickman

COMPLETE RESPONSE -- MAJOR

ANDA 90-218

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)



APPLICANT: Sandoz Inc.

TEL: (609) 627-8885

ATTN: Srinivasa S Rao

FAX: (609) 395-2792

FROM: Esther Chuh

FDA CONTACT PHONE: (240) 276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated December 26, 2007, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glatiramer Acetate Injection, 20 mg/mL.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.

This will improve document availability to review staff.

We have completed the review of your ANDA and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues in the following attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR AMENDMENT should appear prominently in your cover letter. Upon OGD's acceptance for filing of your ANDA, it was determined that an adequate amount of information was submitted to allow for review of your Bioequivalence and Microbiology data. You will be notified in a separate communication of any further deficiencies identified during our review of your Bioequivalence and Microbiology data. If this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 90-218

APPLICANT: Sandoz Inc.

DRUG PRODUCT: Glatiramer Acetate Injection, 20 mg/mL

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. We have the following general comment with regard to the manufacture of the drug substance:

a. [Redacted] (b) (4)

b. [Redacted]

2. We have the following general comments with regard to the characterization of glatiramer acetate and the demonstration of sameness in Section 3.2.S.3:

a. [Redacted] (b) (4)

b. [Redacted]

c. [Redacted]

3. We have the following specific requests with regard to the characterization of glatiramer acetate as described in Section 3.2.S.3:

a. [Redacted] (b) (4)

i. [Redacted] (b) (4)

[Redacted] (b) (4)

Following this page, 3 pages withheld in full - (b)(4)

s. Drug Substance Specification

i.

(b) (4)

ii.

iii.

iv.

v.

vi.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

1. Please be advised that the review of the remainder of the CMC section of the application is deferred until the deficiencies of the information on drug substance sameness are fully resolved.
2. Your sterility assurance, bioequivalence, and labeling information are pending review. Deficiencies, if any, will be communicated separately.
3. We may require a satisfactory method validation study in an FDA laboratory to support the ANDA and will schedule it at an appropriate time.
4. An acceptable compliance evaluation is necessary for approval and we have requested an evaluation from the Office of Compliance.

Sincerely,

{See appended electronic signature page.}

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Michael Smela
9/15/2008 03:05:55 PM
For Rashmikant M. Patel, Ph.D.



ANDA 90-218

Sandoz Inc.
Attention: Srinivasa S. Rao
506 Carnegie Center, Suite 400
Princeton, NJ 08540

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated July 3, 2008 and your correspondence dated July 7, 2008.

NAME OF DRUG: Glatiramer Acetate Injection,
20 mg/mL, 1 mL Pre-filled Syringes

DATE OF APPLICATION: December 26, 2007

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 27, 2007

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:
 - 1) Each owner of the patent or the representative designated by the owner to receive the notice;
 - 2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.
 - 3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.
- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (240) 276-8419.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Esther Chuh
Project Manager
(240) 276-8530

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Martin Shimer
7/9/2008 07:21:13 AM
Signing for Wm Peter Rickman

ADDITIONAL COMMENTS REGARDING THE ANDA:

7/3/2008 Tcon Srinivasa S. Rao (609-627-8885)

*1. Please provide certification that you will comply with the requirements under 21 CFR 314.95 (a) and (c)**Adequate for filing per 7/7/08 correspondence**2. The RLD pre-filled syringe label is not legible. Please submit a legible copy.**Adequate for filing per 7/7/08 correspondence*

Notes:

1. The sponsor does not have Type 2 DMF reference and does not have EBR nor MBR. Mike Smela was contacted regarding the requirement, and he mentioned that we can request it but have no legal authority. We can accept a detailed description of the manufacturing process. This description can be found in section 3.2.S.2.2.

2. The decision was made by CDER on 7/1/2008 to allow the filing of this ANDA as a 505(j)

**MODULE 1
ADMINISTRATIVE**

ACCEPTABLE

1.1	1.1.2 Signed and Completed Application Form (356h) (original signature) (Check Rx/OTC Status) RX YES Form FDA 3674 submitted 9.a.	<input checked="" type="checkbox"/>
1.2	Cover Letter Dated: DECEMBER 26, 2007	<input checked="" type="checkbox"/>
*	Table of Contents (paper submission only) YES	<input checked="" type="checkbox"/>
1.3.2	Field Copy Certification (original signature) esub (N/A for E-Submissions)	<input checked="" type="checkbox"/>
1.3.3	Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other: 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) none	<input checked="" type="checkbox"/>
1.3.4	Financial Certifications Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) NA or Disclosure Statement (Form FDA 3455) NO	<input checked="" type="checkbox"/>

<p>1.3.5</p>	<p>1.3.5.1 Patent Information Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations</p> <p>1.3.5.2 Patent Certification 1. Patent number(s) 5981589 MAY 24,2014 PIV 6054430 MAY 24,2014 PIV 6342476 MAY 24,2014 U-441 PIV 6362161 MAY 24,2014 U-441 PIV 6620847 MAY 24,2014 PIV 6939539 MAY 24,2014 PIV 7199098 MAY 24,2014 PIV U-441 METHOD OF TREATING MS BY ADMINISTERING COPAXONE</p> <p><i>1. Please provide certification that you will comply with the requirements under 21 CFR 314.95 (a) and (c)</i> <i>Adequate for filing per 7/7/08 correspondence</i></p> <p>2. Paragraph: (Check all certifications that apply) MOU <input type="checkbox"/> PI <input type="checkbox"/> PII <input type="checkbox"/> PIII <input type="checkbox"/> PIV <input checked="" type="checkbox"/> (Statement of Notification) <input type="checkbox"/></p> <p>3. Expiration of Patent(s): 5-24-2014 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity?</p> <p>4. Exclusivity Statement: YES</p>	<p><input checked="" type="checkbox"/></p>
<p>1.4.1</p>	<p>References Letters of Authorization</p> <p>1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient API CMC information submitted in ANDA b. Type III DMF authorization letter(s) for container closure DMFs (b) (4)</p> <p>2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) NA</p>	<p><input checked="" type="checkbox"/></p>
<p>1.12.11</p>	<p>Basis for Submission NDA# : 20-622 Ref Listed Drug: COPAXONE Firm: TEVA ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1</p>	<p><input checked="" type="checkbox"/></p>

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

<p>1.12.12</p>	<p>Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients Same as RLD 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength Same as RLD</p>	<p><input checked="" type="checkbox"/></p>
<p>1.12.14</p>	<p>Environmental Impact Analysis Statement YES</p>	<p><input checked="" type="checkbox"/></p>

1.12.15	Request for Waiver Request for Waiver of In-Vivo BA/BE Study(ies): YES	☒
1.14.1	Draft Labeling (Mult Copies N/A for E-Submissions) 1.14.1.1 4 copies of draft (each strength and container) submitted 1.14.1.2 1 side by side labeling comparison of containers and carton with all differences annotated and explained submitted 1.14.1.3 1 package insert (content of labeling) submitted electronically submitted ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	Listed Drug Labeling 1.14.3.1 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained submitted 1.14.3.3 1 RLD label and 1 RLD container label submitted <i>2. The RLD pre-filled syringe label is not legible. Please submit a legible copy.</i> <i>Adequate for filing per 7/7/08 correspondence</i>	☒

<p>2.3</p>	<p>Quality Overall Summary (QOS) E-Submission: PDF submitted Word Processed e.g., MS Word submitted</p> <p>A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/</p> <p>Question based Review (QbR)</p> <p>2.3.S Drug Substance (Active Pharmaceutical Ingredient) 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards or Materials 2.3.S.6 Container Closure System 2.3.S.7 Stability</p> <p>2.3.P Drug Product 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards or Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability</p>	<p><input checked="" type="checkbox"/></p>
<p>2.7</p>	<p>Clinical Summary (Bioequivalence) E-Submission: PDF Word Processed e.g., MS Word</p> <p>2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods 2.7.1.1 Background and Overview Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data 2.7.1.2 Summary of Results of Individual Studies Table 5. Summary of In Vitro Dissolution 2.7.1.3 Comparison and Analyses of Results Across Studies Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data 2.7.1.4 Appendix 2.7.4.1.3 Demographic and Other Characteristics of Study Population Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study 2.7.4.2.1.1 Common Adverse Events Table 8. Incidence of Adverse Events in Individual Studies</p>	<p><input type="checkbox"/></p>

3.2.S DRUG SUBSTANCE



ACCEPTABLE

<p>3.2.S.1</p>	<p>General Information 3.2.S.1.1 Nomenclature submitted 3.2.S.1.2 Structure submitted 3.2.S.1.3 General Properties submitted</p>	<p>☒</p>						
<p>3.2.S.2</p>	<p>Manufacturer 3.2.S.2.1 Manufacturer(s) (Includes contract manufacturers and testing labs) Drug Substance (Active Pharmaceutical Ingredient) 1. Addresses of bulk manufacturers (b) (4) not added. See email from OC. 2. Manufacturing Responsibilities submitted 3. Type II DMF number for API CMC information for API in ANDA 4. CFN or FEI numbers submitted</p>	<p>☒</p>						
<p>3.2.S.3</p>	<p>Characterization submitted</p>	<p>☒</p>						
<p>3.2.S.4</p>	<p>Control of Drug Substance (Active Pharmaceutical Ingredient) 3.2.S.4.1 Specification Testing specifications and data from drug substance manufacturer(s) submitted 3.2.S.4.2 Analytical Procedures submitted 3.2.S.4.3 Validation of Analytical Procedures 1. Spectra and chromatograms for reference standards and test samples Copies of the IR and UV spectra for Lot #077K7277 in section 2.3.S.3.2.1 2. Samples-Statement of Availability and Identification of: a. Drug Substance submitted b. Same lot number(s) Table 53. Glatiramer Acetate Sample</p> <table border="1" data-bbox="370 1224 1390 1350"> <thead> <tr> <th>Lot Number (Exhibit batch)</th> <th># Samples</th> <th>Quantity per Sample</th> </tr> </thead> <tbody> <tr> <td>077K7277</td> <td>3</td> <td>50 grams</td> </tr> </tbody> </table> <p>3.2.S.4.4 Batch Analysis 1. COA(s) specifications and test results from drug substance mfr(s) 2. Applicant certificate of analysis submitted Lot #077K7277 second demonstration batch Lot 087K7253 COA not submitted 3.2.S.4.5 Justification of Specification submitted</p>	Lot Number (Exhibit batch)	# Samples	Quantity per Sample	077K7277	3	50 grams	<p>☒</p>
Lot Number (Exhibit batch)	# Samples	Quantity per Sample						
077K7277	3	50 grams						
<p>3.2.S.5</p>	<p>Reference Standards or Materials submitted</p>	<p>☒</p>						
<p>3.2.S.6</p>	<p>Container Closure Systems submitted</p>	<p>☒</p>						
<p>3.2.S.7</p>	<p>Stability submitted</p>	<p>☒</p>						

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

<p>3.2.P.1</p>	<p>Description and Composition of the Drug Product 1) Unit composition submitted 2) Inactive ingredients are appropriate per IIG Yes</p>	<p>☒</p>
<p>3.2.P.2</p>	<p>Pharmaceutical Development Pharmaceutical Development Report</p>	<p>☒</p>
<p>3.2.P.3</p>	<p>Manufacture 3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es) of the Facility(ies) submitted 2. CGMP Certification: YES 3. Function or Responsibility submitted 4. CFN or FEI numbers submitted 3.2.P.3.2 Batch Formula Batch Formulation submitted Table 1. Batch Formula for Glatiramer Acetate Injection  (b) (4) Content from the COA. 3.2.P.3.3 Description of Manufacturing Process and Process Controls 1. Description of the Manufacturing Process submitted 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified MBR TY (b) (4) syringes 3. If sterile product: (b) (4) 4. Reprocessing Statement submitted 3.2.P.3.4 Controls of Critical Steps and Intermediates submitted 3.2.P.3.5 Process Validation and/or Evaluation 1. Microbiological sterilization validation  (b) (4)</p>	<p>☒</p>

3.2.P.4	Controls of Excipients (Inactive Ingredients) Source of inactive ingredients identified submitted 3.2.P.4.1 Specifications 1. Testing specifications (including identification and characterization) submitted 2. Suppliers' COA (specifications and test results) submitted 3.2.P.4.2 Analytical Procedures per USP/NF 3.2.P.4.3 Validation of Analytical Procedures 3.2.P.4.4 Justification of Specifications Applicant COA	☒
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MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

<p>3.2.P.5</p>	<p>Controls of Drug Product 3.2.P.5.1 Specification(s) submitted 3.2.P.5.2 Analytical Procedures submitted 3.2.P.5.3 Validation of Analytical Procedures Samples - Statement of Availability and Identification of: 1. Finished Dosage Form submitted 2. Same lot numbers CT0743 3.2.P.5.4 Batch Analysis Certificate of Analysis for Finished Dosage Form submitted CT0743 3.2.P.5.5 Characterization of Impurities submitted 3.2.P.5.6 Justification of Specifications submitted</p>	<p><input checked="" type="checkbox"/></p>
<p>3.2.P.7</p>	<p>Container Closure System 1. Summary of Container/Closure System (if new resin, provide data) submitted 2. Components Specification and Test Data submitted COA in section 3.2.R.1.P.2 3. Packaging Configuration and Sizes 1 mL PFS 4. Container/Closure Testing 5. Source of supply and suppliers address submitted</p>	<p><input checked="" type="checkbox"/></p>
<p>3.2.P.8</p>	<p>3.2.P.8.1 Stability (Finished Dosage Form) 1. Stability Protocol submitted submitted 2. Expiration Dating Period ^(b)₍₄₎ months 3.2.P.8.2 Post-approval Stability and Conclusion Post Approval Stability Protocol and Commitments submitted 3.2.P.8.3 Stability Data 1. 3 month accelerated stability data submitted 2. Batch numbers on stability records the same as the test batch yes</p>	<p><input checked="" type="checkbox"/></p>

MODULE 3

3.2.R Regional Information

ACCEPTABLE

<p>3.2.R (Drug Substance)</p>	<p>3.2.R.1.S Executed Batch Records for drug substance (if available) Not submitted 3.2.R.2.S Comparability Protocols 3.2.R.3.S Methods Validation Package NA Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)</p>	<p><input type="checkbox"/></p>
<p>3.2.R (Drug Product)</p>	<p>3.2.R.1.P.1 Executed Batch Records Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation Theoretical Yield (b) (4) syringes Actual Yield (b) (4) syringes 3.2.R.1.P.2 Information on Components submitted 3.2.R.2.P Comparability Protocols 3.2.R.3.P Methods Validation Package Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)</p>	<p><input checked="" type="checkbox"/></p>

MODULE 5

CLINICAL STUDY REPORTS

ACCEPTABLE

<p>5.2</p>	<p>Tabular Listing of Clinical Studies E-Submission: PDF Word Processed e.g., MS Word</p>	<p><input type="checkbox"/></p>
<p>5.3.1 (complete study data)</p>	<p>Bioavailability/Bioequivalence 1. Formulation data same? a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) 2. Lot Numbers of Products used in BE Study(ies): 3. Study Type: IN-VIVO PK STUDY(IES) (Continue with the appropriate study type box below)</p>	<p><input type="checkbox"/></p>

	<p>5.3.1.2 Comparative BA/BE Study Reports</p> <ol style="list-style-type: none"> 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: <ul style="list-style-type: none"> Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations <p>5.3.1.3 In Vitro-In-Vivo Correlation Study Reports</p> <ol style="list-style-type: none"> 1. Summary Bioequivalence tables: <ul style="list-style-type: none"> Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study <p>5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies</p> <ol style="list-style-type: none"> 1. Summary Bioequivalence table: <ul style="list-style-type: none"> Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples <p>5.3.7 Case Report Forms and Individual Patient Listing</p>	<input type="checkbox"/>
<p>5.4</p>	<p>Literature References</p>	
	<p>Possible Study Types:</p>	
<p>Study Type</p>	<p>IN-VIVO PK STUDY(IES) (i.e., fasting/fed/sprinkle) NA</p> <ol style="list-style-type: none"> 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: NO 	<input type="checkbox"/>
<p>Study Type</p>	<p>IN-VIVO BE STUDY with CLINICAL ENDPOINTS NO</p> <ol style="list-style-type: none"> 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted 	<input type="checkbox"/>
<p>Study Type</p>	<p>IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) NO</p> <ol style="list-style-type: none"> 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution: 	<input type="checkbox"/>

Study Type	<p style="text-align: center;">NASALLY ADMINISTERED DRUG PRODUCTS</p> <ol style="list-style-type: none"> 1. <u>Solutions</u> (Q1/Q2 sameness): <ol style="list-style-type: none"> a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. <u>Suspensions</u> (Q1/Q2 sameness): <ol style="list-style-type: none"> a. In-Vivo PK Study <ol style="list-style-type: none"> 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points <ol style="list-style-type: none"> 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo (p<0.05) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 	<input type="checkbox"/>
Study Type	<p style="text-align: center;">IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies)</p> <ol style="list-style-type: none"> 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125) 	<input type="checkbox"/>
Study Type	<p style="text-align: center;">TRANSDERMAL DELIVERY SYSTEMS</p> <ol style="list-style-type: none"> 1. <u>In-Vivo PK Study</u> <ol style="list-style-type: none"> 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. <u>Adhesion Study</u> 3. <u>Skin Irritation/Sensitization Study</u> 	<input type="checkbox"/>

Search results from the "OB_Rx" table for query on "020622."

Active Ingredient: GLATIRAMER ACETATE
Dosage Form;Route: FOR SOLUTION; SUBCUTANEOUS
Proprietary Name: COPAXONE
Applicant: TEVA
Strength: 20MG/VIAL
Application Number: 020622
Product Number: 001
Approval Date: Dec 20, 1996
Reference Listed Drug: Yes
RX/OTC/DISCN: RX
TE Code:

Patent and Exclusivity Info for this product: [View](#)

Active Ingredient: GLATIRAMER ACETATE
Dosage Form;Route: INJECTABLE; SUBCUTANEOUS
Proprietary Name: COPAXONE
Applicant: TEVA
Strength: 20MG/ML
Application Number: 020622
Product Number: 002
Approval Date: Feb 12, 2002
Reference Listed Drug: Yes
RX/OTC/DISCN: RX
TE Code:

Patent and Exclusivity Info for this product: [View](#)

[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through January, 2008

Patent and Generic Drug Product Data Last Updated: February 27, 2008

Patent and Exclusivity Search Results from query on Appl No 020622 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
020622	002	5981589	MAY 24,2014			
020622	002	6054430	MAY 24,2014			
020622	002	6342476	MAY 24,2014			U-441
020622	002	6362161	MAY 24,2014			U-441
020622	002	6620847	MAY 24,2014	Y		
020622	002	6939539	MAY 24,2014	Y		
020622	002	7199098	MAY 24,2014	Y		

Exclusivity Data

There is no unexpired exclusivity for this product.

90-218 - Message (Rich Text)

Reply Reply to All Forward

File Edit View Insert Format Tools Actions Help Adobe PDF

You replied on 2/28/2008 11:11 AM.

From: Shelton, Lisa Sent: Thu 2/28/2008 11:04 AM
To: Chen, Peter
Cc:
Subject: 90-218

For ANDA 90-218, I located the (b) (4) validation) in Section 3.2.P.3.5, Appendix I (32p35-process.pdf). Micro gives it a green light. :)

Lisa

Table 1. Composition of Glatiramer Acetate Injection

Component	Amount per Syringe	Function	Quality Standard
Glatiramer Acetate	20 mg	Active Pharmaceutical Ingredient	N/A
Mannitol	40 mg	(b) (4)	USP
Water for Injection	q.s. to 1 mL		USP

N020622 PRODUCT DETAILS
 Prod:002 TE: Rx/OTC:RX Trade:COPAXONE

Received 22-MAY-2001	Approval APPEF/12-FEB-2002	Discontinued	Withdrawal
-------------------------	-------------------------------	--------------	------------

Current Dosage Form(s) Route(s) of Administration
 SOLUTION, INJECTION SUBCUTANEOUS

Part 01

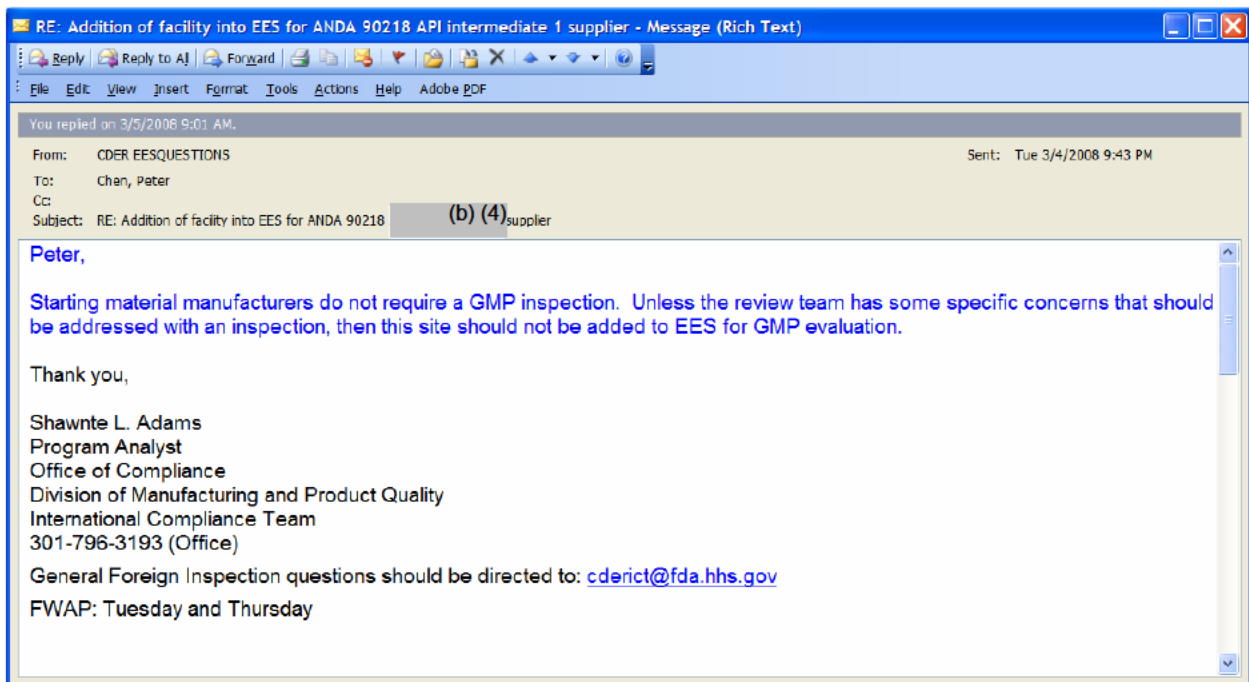
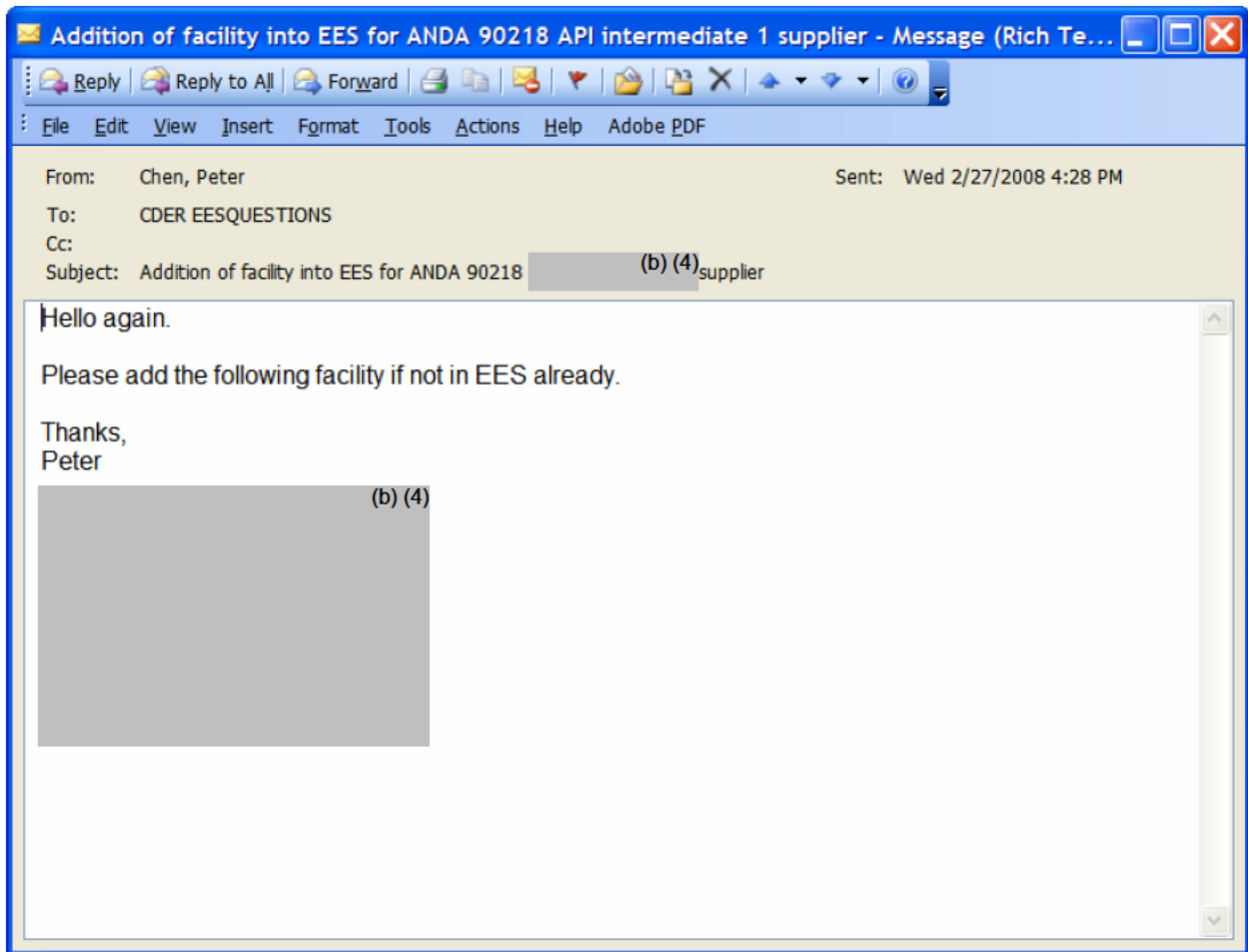
Ingredient Name	POTENCY	Type
GLATIRAMER ACETATE	20MG/1ML	ACTIVE
MANNITOL	40MG/1ML	INACTIVE

UP/DOWN: Move to previous/next product RETURN: Move cursor to next field
 (P)F2: Help (P)F4: Return to previous screen
 ESC-P: Print NDA

Count: 1 v <Replace>

1(002,007) Printer: Ready

ONLINE MICKEY.CDER.FDA.GOV VT420 VT220 SCRIPT TRANSFER INSERT NUM HOLD CAPS COMPOSE 05:10:44



Message (Rich Text)

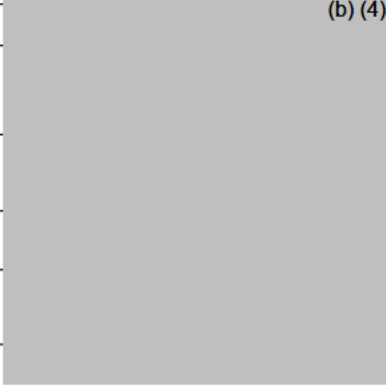
Reply | Reply to All | Forward | [Icons]

File Edit View Insert Format Tools Actions Help Adobe PDF

From: Chen, Peter Sent: Wed 2/27/2008 6:26 PM
To: CDER EESQUESTIONS
Cc:
Subject: Addition of another facility into EES for 90-218

Hello,

Please add the following as a drug product manufacturer:

Manufacturer:	 (b) (4)
Address:	
FDA Registration Number:	
Responsibility:	
Name of Contact Person:	
Telephone Number for Contact Person:	


Thanks,
Peter

Table 45. Exhibit Batch CT0743 Solution Reconciliation

(b) (4)



Table 46. Exhibit Batch CT0743 Filled Syringe Reconciliation

	# Syringes	Yields
Filled Syringes		(b) (4)
Total Rejected Units		
Units Sampled		
Total to Storage		
Total Accounted For		
Percent Reconciliation		100%

Establishment Evaluation System

File Edit Search Navigate Options Window Help

Application Drawer

Application Establishments Status Milestones Comments Contacts Product

Application: N 90218/000 Sponsor: SANDOZ

Drug Name: GLATIRAMER ACETATE

Establishment CFN / FEI	Name	Profile Code	Name	Last Milestone Date	Last Compliance Status	Date	OAI Alert
(b) (4)		CTL	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	
		CTL	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	
		SVS	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	
		CSN	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	
		CSN	SUBMITTED TO DO	03-MAR-2008	PN	27-FEB-2008	
		CTL	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	

Overall Compliance:

Date Recommendation

Save Close

Record: 6/7 <OSC> <DBG>

Establishment Evaluation System

File Edit Search Navigate Options Window Help

Application Drawer

Application Establishments Status Milestones Comments Contacts Product

Application: N 90218/000 Sponsor: SANDOZ

Drug Name: GLATIRAMER ACETATE

Establishment CFN / FEI	Name	Profile Code	Name	Last Milestone Date	Last Compliance Status	Date	OAI Alert
(b) (4)		CTL	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	
		SVS	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	
		CSN	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	
		CSN	SUBMITTED TO DO	03-MAR-2008	PN	27-FEB-2008	
		CTL	OC RECOMMENDATION	28-FEB-2008	AC	28-FEB-2008	
		SVS	SUBMITTED TO OC	02-JUL-2008	PN	02-JUL-2008	

Overall Compliance:

Date Recommendation

Save Close

Record: 7/7 <OSC> <DBG>



Srinivasa S. Rao, Pharm. D.
Director,
Regulatory Affairs

Sandoz Inc.
506 Carnegie Centre
Suite 400
Princeton, NJ 08540

Tel: 609-627-8885 (Direct)
Fax: 609-395-2792

July 7, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **ANDA 090218**
Glatiramer Acetate Injection 20 mg/mL

Dear Sir/Madam:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act, and in accordance with 21 CFR parts 314.92 and 314.94, enclosed is an amendment to the Sandoz Inc. original Abbreviated New Drug Application for Glatiramer Acetate Injection, 20 mg/mL, originally filed on December 26, 2007.

Reference is made to your letter dated July 3, 2008. A response to your administrative deficiencies is provided below:

1. **FDA Comment:**

Please provide certification that you will comply with requirements under 21 CFR 314.95 (a) and (c).

Sandoz Response:

The certification we will comply with requirements under 21 CFR 314.95 (a) and (c) can be found in Section 1.3.5.2 Patent Certifications (page 1).

2. **FDA Comment:**

The RLD pre-filled syringe label is not legible. Please submit a legible copy.

Sandoz Response:

A legible copy can be found in Section 1.14.1.2 Annotated Draft Labeling Text (page 6).



Sandoz Inc.
505 Carnegie Centre
Suite 400
Princeton, NJ 08540

Tel: 609-627-8885 (Direct)
Fax: 609-395-2792

This information is submitted for your review.

Sincerely,

 7/7/08

Srinivasa S. Rao, Pharm. D.
Director, Regulatory Affairs
Sandoz Inc.



**DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION**

**Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with
Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))**


(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

Form Approved: OMB No. 0910-0616
Expiration Date: 06-30-2008
See OMB Statement on Reverse

SPONSOR/APPLICANT/SUBMITTER INFORMATION									
<p>1. NAME OF SPONSOR/APPLICANT/SUBMITTER</p> <div style="border: 1px solid black; padding: 2px; min-height: 20px;">Sandoz Inc.</div>	<p>2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES</p> <div style="border: 1px solid black; padding: 2px; min-height: 20px;">07/07/2008</div>								
<p>3. ADDRESS (Number, Street, State, and Zip Code)</p> <div style="border: 1px solid black; padding: 2px; min-height: 40px;">506 Carnegie Centre Suite 400 Princeton, NJ 08540</div>	<p>4. TELEPHONE AND FAX NUMBER (Include Area Code)</p> <table style="width:100%; border-collapse: collapse;"> <tr> <td style="width:10%; border: 1px solid black;">(T)</td> <td style="border: 1px solid black; padding: 2px;">+1 (609) 627-8885</td> </tr> <tr> <td style="border: 1px solid black;">(F)</td> <td style="border: 1px solid black; padding: 2px;">+1 (609) 395-2792</td> </tr> </table>	(T)	+1 (609) 627-8885	(F)	+1 (609) 395-2792				
(T)	+1 (609) 627-8885								
(F)	+1 (609) 395-2792								
PRODUCT INFORMATION									
<p>5. FOR DRUGS/BIOLOGICS: Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s) FOR DEVICES: Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s) (Attach extra pages as necessary)</p> <table style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%; border: 1px solid black; padding: 2px;">Glatiramer Acetate Injection 20 mg/mL</td> <td style="width:50%; border: 1px solid black; height: 20px;"></td> </tr> <tr> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> </tr> <tr> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> </tr> <tr> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> </tr> </table>		Glatiramer Acetate Injection 20 mg/mL							
Glatiramer Acetate Injection 20 mg/mL									
APPLICATION/SUBMISSION INFORMATION									
<p>6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES</p> <p> <input type="checkbox"/> IND <input type="checkbox"/> NDA <input checked="" type="checkbox"/> ANDA <input type="checkbox"/> BLA <input type="checkbox"/> PMA <input type="checkbox"/> HDE <input type="checkbox"/> 510(k) <input type="checkbox"/> PDP <input type="checkbox"/> Other </p>									
<p>7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER (If number previously assigned)</p> <table style="width:100%; border-collapse: collapse;"> <tr> <td style="border: 1px solid black; padding: 2px; width: 15%;">90,218</td> <td style="border: 1px solid black; width: 15%;"></td> <td style="border: 1px solid black; width: 15%;"></td> <td style="border: 1px solid black; width: 15%;"></td> <td style="border: 1px solid black; width: 15%;"></td> <td style="border: 1px solid black; width: 15%;"></td> </tr> </table>		90,218							
90,218									
<p>8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES</p> <div style="border: 1px solid black; padding: 2px; min-height: 20px;">1</div>									
CERTIFICATION STATEMENT/INFORMATION									
<p>9. CHECK ONLY ONE OF THE FOLLOWING BOXES (See instructions for additional information and explanation)</p> <p> <input checked="" type="checkbox"/> A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial. </p> <p> <input type="checkbox"/> B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies. </p> <p> <input type="checkbox"/> C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met. </p>									
<p>10. IF YOU CHECKED BOX C, IN # 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES (Attach extra pages as necessary)</p> <p>NCT Number(s)</p> <table style="width:100%; border-collapse: collapse;"> <tr> <td style="border: 1px solid black; width: 20%;"></td> <td style="border: 1px solid black; width: 20%;"></td> <td style="border: 1px solid black; width: 20%;"></td> <td style="border: 1px solid black; width: 20%;"></td> <td style="border: 1px solid black; width: 20%;"></td> </tr> </table>									

The undersigned declares to the best of her or his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 2626 (5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act.

Warning: A willfully and knowingly false statement is a criminal offense, U.S. Code Title 18, section 1001.

<p>11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (SIGN)</p> 	<p>12. NAME AND TITLE OF THE PERSON WHO SIGNED IN #11</p> <p>Srinivasa S. Rao, Pharm.D.</p> <p>Director, Regulatory Affairs</p>
<p>13. ADDRESS (Number, Street, State, and Zip Code) (of person identified in #11 & 12)</p> <p>506 Carnegie Centre Suite 400 Princeton, NJ 08540</p>	<p>14. TELEPHONE AND FAX NUMBER (Include Area Code)</p> <p>(T) +1 (609) 627-8885</p> <p>(F) +1 (609) 395-2792</p>

15. DATE OF CERTIFICATION July 7, 2008

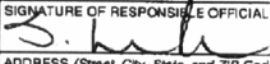
Paperwork Reduction Act Statement

Public Reporting Burden for this collection of information is estimated to average 15 minutes and 45 minutes (depending on the type of application/submission) per response, including time for reviewing instructions. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to the applicable address below.

Food and Drug Administration Center for Drug Evaluation and Research Central Document Room Form No. FDA 3674 5901-B Ammendale Road Beltsville, MD 20705-1266	Food and Drug Administration Center for Biologics Evaluation and Research 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration Center for Devices and Radiological Health Program Operations Staff (HFZ-403) 9200 Corporate Blvd. Rockville, MD 20850
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An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information, unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>		Form Approved: OMB No. 0910-0130 Expiration Date: April 30, 2009 See OMB Statement on page 2.
		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT SANDOZ, INC.		DATE OF SUBMISSION 07/07/2008
TELEPHONE NO. (Include Area Code) (609) 627-8885		FACSIMILE (FAX) Number (Include Area Code) (609) 395-2792
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 506 Carnegie Center Suite 400 Princeton, NJ 08540		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE
PRODUCT DESCRIPTION		
NEW DRUG OR AN ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) ANDA - 090218		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Glatiramer Acetate		PROPRIETARY NAME (trade name) IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)		CODE NAME (if any)
DOSAGE FORM: Injection	STRENGTHS: 20 mg/mL	ROUTE OF ADMINISTRATION: Subcutaneous Injection
(PROPOSED) INDICATION(S) FOR USE: Reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis		
APPLICATION INFORMATION		
APPLICATION TYPE (check one) <input type="checkbox"/> NEW DRUG APPLICATION (NDA, 21 CFR 314.50) <input checked="" type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: Copaxone® Holder of Approved Application: Teva		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRE-SUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CBE <input type="checkbox"/> CBE-30 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION Original application		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED 1 CD	THIS APPLICATION IS <input type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input checked="" type="checkbox"/> ELECTRONIC	
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready. See attachment A for a list of all establishments. All sites are ready for inspection.		
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)		
DMF (b) (4) DMF DMF		

This application contains the following items: <i>(Check all that apply)</i>		
<input checked="" type="checkbox"/>	1. Index	
<input checked="" type="checkbox"/>	2. Labeling <i>(check one)</i>	<input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(l)(1); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input checked="" type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input type="checkbox"/>	20. OTHER <i>(Specify)</i>	
CERTIFICATION		
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:		
<ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 620. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 680, and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. 5. Regulations on making changes in application in FD&C Act section 508A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. 7. Local, state and Federal environmental impact laws. 		
If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.		
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.		
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Srinivasa S. Rao, Pharm.D., Director, Regulatory Affairs	DATE 07/07/2008
ADDRESS <i>(Street, City, State, and ZIP Code)</i> Sandoz, Inc., 506 Carnegie Center, Suite 400, Princeton, NJ 08540		Telephone Number (609) 627-8885
Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:		
Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (HFD-143) Central Document Room 5901-B Ammendale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HBM-99) 1401 Rockville Pike Rockville, MD 20852-1448	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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this page is the manifestation of the electronic signature.**

/s/

Martin Shimer

7/9/2008 07:21:34 AM